The Dissertation Committee for Henry Matthew Lehrer Certifies that this is the approved version of the following Dissertation:

Psychosocial Stress, Hypothalamic Pituitary Adrenal (HPA) Axis Function, and Cardiometabolic Health

Committee:

Mary Steinhardt, Supervisor

John Bartholomew

Molly Bray

Tasha Beretvas

Jaimie Davis

Julie Maslowsky

Psychosocial Stress, Hypothalamic Pituitary Adrenal (HPA) Axis Function, and Cardiometabolic Health

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Henry Matthew Lehrer

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Abstract

Psychosocial Stress, Hypothalamic Pituitary Adrenal (HPA) Axis Function, and Cardiometabolic Health

Henry Matthew Lehrer, Ph.D.

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Supervisor: Mary Steinhardt

This dissertation examines the contribution of various psychological and social stressors to indicators of cardiovascular and metabolic function and disease. It also investigates the role of altered hypothalamic pituitary adrenal (HPA) axis activity as a mechanism by which psychosocial stress may influence cardiometabolic health. Grounded in the framework of the allostatic load model, studies 1-3 build on each other to assess the interplay between various types of stress, HPA axis indicators, and cardiometabolic health outcomes among diverse populations. Study 1 examines the association of perceived everyday discrimination and hair cortisol concentration, a stable indicator of retrospective cortisol output indexed over several months. The analyses focus on racial group differences, finding that perceived discrimination scores were associated with elevated hair cortisol concentration for African American adults but not White adults. Given that both groups reported similar discrimination frequency scores, this finding suggests that more qualitative characteristics of discrimination may be particularly salient to HPA axis output among African Americans. Study 2 moves one step past the stress-HPA axis association by examining the role that elevated HPA axis

activity plays in the association between perceived stress and metabolic syndrome severity. This study found that psychological resilience protected against the association of elevated perceived stress with increased metabolic syndrome severity via elevated hair cortisol concentration. Study 3 uses the same resilience-based framework as study 2, but does so in a national longitudinal cohort of U.S. adults. Using daily diary entries and salivary cortisol analysis, this study examines unique effects of daily stressor frequency and severity on cardiovascular and metabolic disease prevalence 5-8 years later. Study 3 also tests whether flattened diurnal salivary cortisol slopes mediator effects of stressor frequency and severity on cardiometabolic conditions, and examines a latent resilience resources variable as a potential buffer of the daily stress-cardiometabolic disease relationship. Findings indicate that greater perceived stressor severity and flattened diurnal cortisol slopes predict greater cardiometabolic disease prevalence later in life. Taken together, this collection of studies provides evidence supporting the contribution of greater psychosocial stress to impaired cardiovascular and metabolic health, and suggests that the HPA axis plays a significant role.

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Chapter 1: General Introduction

The mounting healthcare burden due to cardiovascular (e.g., heart disease, stroke, hypertension) and metabolic (e.g., type 2 diabetes, obesity) diseases is the preeminent health-related challenge facing the United States in the 21st century (The U.S. Burden of Disease Collaborators et al., 2018). Behavioral risk factors including smoking, alcohol consumption, dietary intake, exercise, and sleep receive a large share of research and funding in efforts to prevent cardiometabolic diseases, but prevalence of and mortality due to these conditions continues to rise. Elevated psychological and social stress also contributes to the onset of cardiometabolic disease (Hackett & Steptoe, 2016) and is experienced frequently in the population (Almeida, Wethington, & Kessler, 2002), but strategies to mitigate detrimental effects of psychosocial stress on cardiometabolic health remain to be fully leveraged in lifestyle-based prevention programs. This is due in part to a limited understanding of 1) which types/characteristics of stress (e.g., discrimination, general stress, stress severity) are most strongly associated with cardiometabolic health, 2) mechanisms by which different facets of stress impact cardiometabolic health, and 3) which, if any, psychosocial attributes protect against the contribution of psychosocial stress to poor cardiometabolic health.

According to the allostatic load model (Figure 1), perceptions of stress elicit physiologic responses (e.g., increased cortisol, catecholamine, and cytokine production) to handle an impending challenge. These responses, collectively called allostasis (i.e., maintaining stability through change), are adaptive in the short term to ensure survival during threatening situations. However, if they are repeatedly engaged without time for proper recovery, the likelihood of wear and tear on the physiologic systems (allostatic load) increases, which can eventually lead to disease (McEwen, 1998). A primary pathway by which psychosocial stress is posited to degrade cardiometabolic health is by unfavorably altering hypothalamic pituitary adrenal (HPA) axis function over time. Cortisol, the end product of the HPA axis, elevates circulating levels of glucose, amino acids, and free fatty acids (Rosmond, 2005), increases heart rate and blood pressure (Brotman, Golden, & Wittstein, 2007), and promotes transport of fat cells from peripheral to central stores (Lee, Pramyothin, Karastergiou, & Fried, 2014). When engaged chronically, these cortisol-induced cardiovascular and metabolic responses to stress are hypothesized to contribute to disease. Individual differences related to genetics, development, and life experiences (e.g., race/ethnicity, psychosocial attributes) can moderate associations of perceived stress with the physiological stress response, and may thus represent variables that stress-reduction interventions can be tailored to, or modifiable targets for such programs.

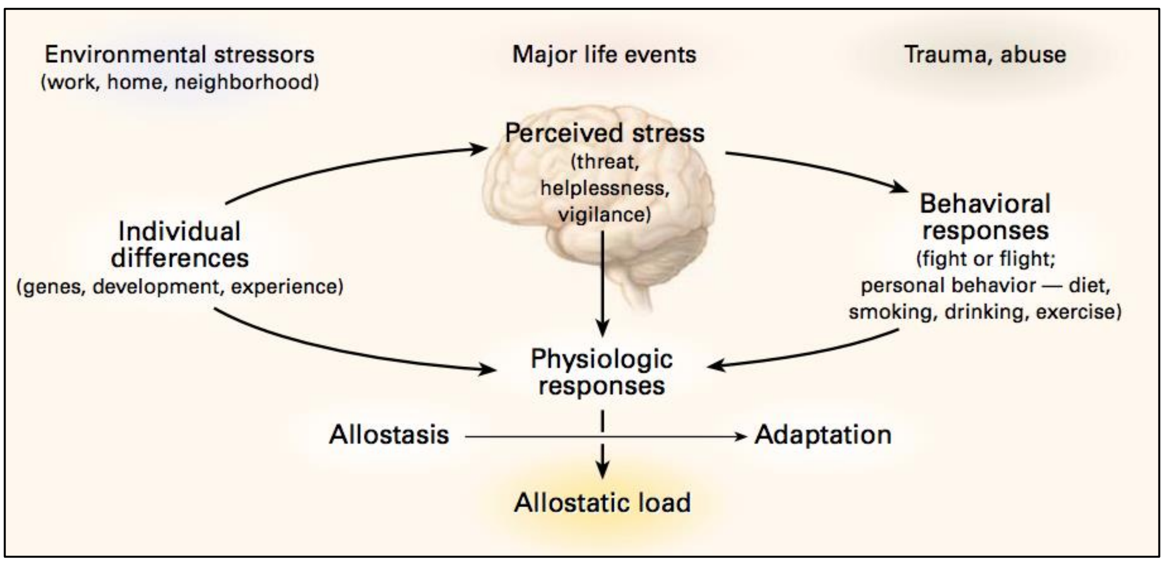

Figure 1. The allostatic load model. McEwen, 1998.

In order to inform more targeted interventions, several gaps in the allostatic load literature must be addressed. For example, perceived discrimination is a known inducer of social threat, and is considered to be more psychologically and physiologically detrimental for racial minority groups, but evidence supporting racial/ethnic differences in the association between discrimination and HPA axis activity is conflicting. This is possibly due to methodological shortcomings that have previously characterized the assessment of chronic HPA axis activation. Considering health outcomes, the indirect association of perceived stress and cardiometabolic health via long-term HPA axis activity is rarely tested in populations most likely to experience stress such as racial/ethnic minority groups. Additionally, metabolic syndrome (MetS) as a proxy of cardiometabolic risk in these groups has also been poorly characterized due to racial/ethnic measurement disparities. The unique contribution of stressor exposure versus stressor severity to HPA axis activity and cardiometabolic disease is poorly understood and is not generalizable, with laboratory studies and cross-sectional research forming a bulk of the literature base. Prospective studies are sorely needed. Finally, considering effective and efficient intervention designs, it is important to understand for whom these processes are most likely to occur. Thus, examining individual differences in potential moderators including the ability to adapt well in the face of adversity and the possession of psychosocial resources known to buffer stress will highlight specific targets to intervene on.

The three studies in this dissertation address these key shortcomings, and are presented in Figure 2. Study 1 investigates the association between perceived everyday discrimination and hair cortisol concentration in a sample of roughly half African American and half White community-dwelling adults. Specifically, it examines whether race moderates the association between perceived discrimination and long-term retrospective HPA axis activity as measured by cortisol levels in scalp hair. Hair cortisol levels are a relatively novel index of HPA axis activity that show promising associations with central adiposity, blood pressure, and diabetes. Study 1 also investigates whether racial group differences in hair cortisol levels are explained by differences in discrimination. Study findings will provide needed evidence to understanding social determinants of racial health disparities.

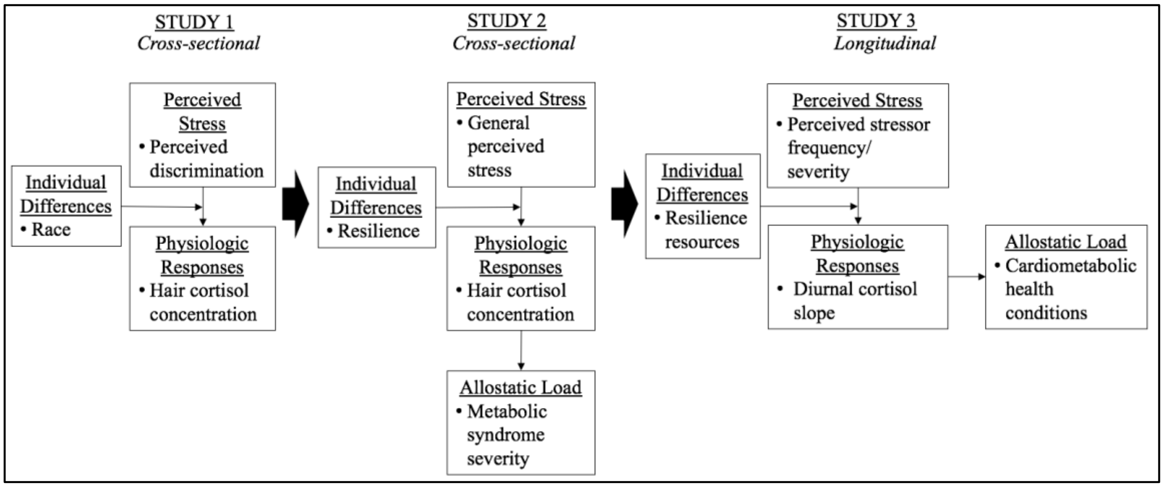

Figure 2. Progression from dissertation studies 1-3, including operationalization of allostatic load constructs.

Moving beyond cortisol as an outcome, Study 2 examines the association of general perceived stress with metabolic syndrome (MetS) severity in a diverse sample of White, African American, and Hispanic adults. Accordingly, MetS will be assessed using a validated MetS severity score based on sex- and race/ethnicity-specific loadings of individual MetS components (Gurka, Lilly, Oliver, & DeBoer, 2014). Further, Study 2 will examine whether hair cortisol levels mediate the association of perceived stress with MetS severity. The association of general perceived stress with hair cortisol is equivocal (Stalder et al., 2017), and may depend on whether individuals possess resilience, or the ability to adapt in the presence of stress. Thus, Study 2 will also examine whether resilience acts as a moderator of the indirect effect of perceived stress on MetS severity via hair cortisol concentration.

Study 3 extends Study 2 to a longitudinal framework by examining the unique influences of daily stressor frequency and daily stressor severity on the prevalence of cardiovascular and metabolic diseases in a large prospective cohort sample of U.S. adults. It additionally examines whether diurnal patterns of HPA axis activity (as measured by salivary cortisol) serve as a mechanism by which heightened stressor exposure and stressor severity influence the prevalence of cardiometabolic disease 5-8 years later. Finally, this study examines whether individuals possessing high levels of resilience resources (e.g., self-esteem, positive reappraisal) are protected from the detrimental effects of greater perceived daily stressor exposure and greater perceived stressor severity on cardiometabolic conditions later in life.

The successful execution of these studies will advance the understanding of whether and how various sources of psychosocial stress and the physiological stress response influence cardiometabolic health, and which individual factors may be worth modifying to prevent or mitigate these damaging processes. The resultant findings will ultimately inform more targeted stress-based interventions for the prevention of cardiovascular and metabolic diseases.

Chapter 2: Study 1 - Race Moderates the Association of Perceived Everyday Discrimination and Hair Cortisol Concentration

ABSTRACT

The influence of discrimination on hypothalamic pituitary adrenal (HPA) axis function is considered to be more pronounced for racial minority versus majority groups, although empirical support for this argument is not strong. This study examined whether the association of perceived discrimination was more strongly associated with long-term, retrospective HPA axis dysfunction (as measured by hair cortisol concentration [HCC]) among African American compared to White adults. Participants included 141 community-dwelling adults (72 White, 69 African American; mean age 45.8 years; 67% females). The Everyday Discrimination Scale assessed perceived discrimination. The first 3 cm of proximal scalp hair were analyzed for HCC using enzyme-linked immunoassay. Associations between race, perceived discrimination and HCC were examined using hierarchical multiple regression. African Americans had higher HCC than Whites, but both groups reported perceived discrimination with similar frequency. Race moderated the association between perceived discrimination and HCC (R^2 interaction = 0.03, p = 0.007), such that perceived discrimination was positively associated with HCC among African Americans (β = 0.28, p = 0.007), but not Whites (β = -0.11, p = 0.274). Perceived discrimination did not mediate the association between race and HCC (β for indirect effect = 0.025, 95% CI [-0.003, 0.087]). Although perceived discrimination did not differ between races, perceived discrimination was positively associated with retrospective levels of cortisol in scalp hair among African Americans but not Whites. This may suggest that characteristics of discrimination other than frequency are particularly salient to HPA axis function among African Americans (e.g., attribution, severity, historical context).

INTRODUCTION

Discrimination, the unequal treatment of an individual or a group of individuals based on real or perceived differences, is a common and health-related stressor for racial and ethnic minorities in the United States (U.S.) (Kessler, Mickelson, & Williams, 1999; Sternthal, Slopen, & Williams, 2011). Discrimination among African Americans is a particularly salient issue for the population, with approximately 92% of African American adults reporting that discrimination exists in the U.S. Among that group, 75% stated that individual discrimination is an important social problem (NPR, Robert Wood Johnson Foundation, & Harvard School of Public Health, 2017). Moreover, discrimination exposure among African Americans is posited to be an important factor linked with disproportionate representation of cardiovascular and metabolic related conditions in the population including hypertension, cardiovascular disease, and diabetes (Lewis, Cogburn, & Williams, 2015; Williams, 2012). Increasing evidence indicates that exposure to discrimination can initiate a series of neuroendocrine responses via the HPA axis that may, if activated chronically, contribute to health disparities (Berger & Sarnyai, 2015). The extent to which the association between perceived discrimination and chronically upregulated HPA axis function differs among racial and ethnic minorities relative to Whites has yet to be established (Busse, Yim, Campos, & Marshburn, 2017).

The biopsychosocial models of racial discrimination and minority health suggest that perceived discrimination engages various biological processes, including the HPA axis (Clark, Anderson, Clark, & Williams, 1999; Myers, 2009). The HPA axis translates perceptions of threat via the hypothalamus, pituitary gland, and finally the adrenal cortex through a cascade of neuroendocrine events, resulting in the production and release of the steroid hormone cortisol into the bloodstream (Tsigos & Chrousos, 2002). Cortisol then acts on a host of physiological systems (e.g., circulatory, immune, digestive) to mobilize biological resources (e.g., glucose, free fatty acids, amino acids) to accommodate the perceived threat. Cortisol secretion typically follows a diurnal pattern, with high levels upon waking that steadily decline throughout the day. Transient increases in cortisol are adaptive in handling environmental stressors, but long-term elevations or flattened declines in cortisol levels throughout the day indicate chronic HPA axis upregulation. Exposure to stress modulates the circadian activity and total output of cortisol, being associated with a flatter decline in cortisol levels across the day, lower waking cortisol levels, and elevated overall cortisol levels (Miller, Chen, & Zhou, 2007). Stressors characterized by social evaluation and uncontrollability, both of which pertain to discrimination, elicit the strongest cortisol responses (Dickerson & Kemeny, 2004).

Though race-based discrimination is more likely experienced by African Americans and other racial minorities, an interracial stress and coping framework posits that discrimination is stressful regardless of the affiliation on which the discrimination was based (e.g., gender, race, age), suggesting that discrimination would influence the HPA axis similarly for racial majority and minority groups (Trawalter, Richeson, & Shelton, 2009). Supporting this argument, more frequently reported perceived discrimination has been associated with flattened salivary cortisol slopes among both African American and White young adults, with the magnitude of the association not differing by race (Skinner, Shirtcliff, Haggerty, Coe, & Catalano, 2011). Other scholars, however, contend that past and present racial tensions in the U.S. could make perceptions of discrimination particularly threatening for racial and ethnic minority individuals, particularly African Americans, increasing the degree to which such perceptions are manifested as altered HPA axis activity (Clark et al., 1999; Williams & Mohammed, 2009).

Among African American young adults, greater perceived everyday discrimination was associated with flatter salivary cortisol slopes compared to European Americans (Zeiders, Hoyt, & Adam, 2014). Similarly, perceived racial discrimination was associated with lower waking salivary cortisol among African American versus White adults (Adam et al., 2015). However, not all research finding racial differences in cortisol indices show that African Americans have markers of altered HPA axis activity, as one study showed that perceived discrimination was associated with steeper diurnal salivary cortisol slopes among African American compared to White adults (Fuller-Rowell, Doan, & Eccles, 2012). Although there is some evidence that discrimination is linked to altered HPA axis function more so among African Americans, it is not conclusive.

These somewhat equivocal findings characterizing the literature on discrimination, cortisol, and race may be due in part to a temporal mismatch inherent in comparing recalled accounts of past discrimination experiences to cortisol obtained acutely from saliva samples, which capture cortisol levels at the time of sampling (Kirschbaum et al., 1990). Fluctuations in cortisol levels due to circadian rhythm or daily variation due to situational factors (e.g., diet, a recent psychological or environmental stressor, infection) suggest that saliva is not ideally suited for capturing retrospective cortisol concentrations that would more closely index the period of time (e.g., the past few months) ascertained by widely-used discrimination questionnaires (Hellhammer et al., 2007).

The analysis of cortisol in scalp hair is a valid indicator of retrospective HPA axis activation over several months (Stalder & Kirschbaum, 2012), but given its relative novelty in psychosocial research, very few studies have examined the association between self-reported discrimination and hair cortisol concentration (HCC). In the

English Longitudinal Study of Aging, comprised of mostly White participants, perceived discrimination due to weight, age, and sex were all positively associated with HCC (Jackson & Steptoe, 2018). Among a racially diverse U.S. sample, lifetime discrimination positively correlated with HCC (O'Brien et al., 2017), and this association was similar across races. However, the discrimination scale used in that study assessed primarily socioeconomic barriers, which may not capture general interpersonal occurrences of unfair treatment towards racial minority individuals surveyed by more commonly-used discrimination measures such as the Everyday Discrimination Scale (Sternthal et al., 2011). A study examining the association of perceived general discrimination with HCC among a racially diverse sample is warranted to advance the current state of discrimination and cortisol research.

The present study examined the association between perceived everyday discrimination and HCC among a sample of African American and White adults. The primary hypothesis (H1) was: Race will moderate the relationship between perceived everyday discrimination and HCC, such that discrimination will be more strongly associated with HCC among African American versus White adults. Additionally, because African Americans have been found to have higher HCC than Whites (Wosu et al., 2015), and often report more frequent discrimination compared to Whites (Kessler et al., 1999; Sternthal et al., 2011), perceived discrimination has been considered a mediating pathway linking race and cortisol levels (Lee et al., 2018). If this is the case, we expect that African Americans will have higher HCC than Whites, and that discrimination frequency will at least partially account for the association between race and HCC. Thus, the secondary hypothesis (H2) is: perceived discrimination will partially mediate the association of African American race and HCC, such that African American race is associated with elevated HCC via increased perceived discrimination.

METHODS

Participants and Procedures

Participants were 141 community-dwelling adults (72 White, 69 African American, mean age 45.8 years, 67% females) recruited through flyers posted on campus, at neighborhood establishments, and on a university research website. Exclusion criteria were baldness/shaved head, pregnant/lactating, or use of glucocorticoid-containing medication. Participants provided written informed consent approved by the Institutional Review Board and were compensated $20 for their time. All study variables were assessed during a single study visit.

Measures

Demographics and hair hygiene

Demographic variables included age, sex (0 = male, 1 = female), and annual household income (from 1 = less than $20,000 to 5 = $100,000 or more, in $20,000 increments). Hair hygiene included number of hair washes/week and use of treatments (conditioners, bleach, permanent wave, straightening) during the three months preceding the study.

Perceived everyday discrimination

Perceived everyday discrimination was assessed using the 5-item version (Sternthal et al., 2011) of the Everyday Discrimination Scale (Williams, Yan Yu, Jackson, & Anderson, 1997). Participants were asked “In your day-to-day life, how often have any of the following things happened to you?” such as, “You are treated with less courtesy or respect than other people” and “People act as if they are afraid of you.” Responses included 1 = never, 2 = less than a few times a year, 3 = a few times a year, 4

= a few times a month, 5 = at least once a week, and 6 = almost every day. The Everyday Discrimination Scale score summed the 5 items. Reliability was acceptable (α = .79).

According to scoring instructions, discrimination attribution was asked of participants answering 3 (a few times a year) or higher for any Everyday Discrimination Scale item (n = 80). Participants were asked, “What do you think is the main reason for these experiences? (If more than one applies, please mark “1” for the most significant reason, and “2” for the second-most significant reason).” Responses included ancestry of national origins, gender, race, age, religion, height, weight, some other aspect of your physical appearance, sexual orientation, and education or income level. Ancestry and race were combined into one category.

Hair cortisol

Hair was cut by a professional hairdresser using thinning shears close to the scalp at the posterior vertex. Hair length was measured after stretching to full length and the proximal 3 cm was ground and analyzed as previously described (Hoffman, Karban, Benitez, Goodteacher, & Laudenslager, 2014). Inter- and intra-assay coefficients of variation were 9.2% and 2.8%, respectively.

Physical and psychosocial health covariates

Physical activity was operationalized as “Thinking about the last three months, how many days/week did you perform at least 30 minutes of physical activity?” Waist and hip circumferences were measured to the nearest 0.1 cm using a non-stretchable standard tape measure: 0.1 cm above the iliac crest on a horizontal plane and at the widest portion of the hip, respectively. Waist-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

Emotional stability was measured with two items from the 10-item Personality Inventory (Gosling, Rentfrow, & Swann, 2003). Participants were asked, "I see myself as: anxious, easily upset" and "I see myself as: calm, emotionally stable." Responses ranged from 1 = disagree strongly to 7 = agree strongly. Items were coded such that higher scores represented greater emotional stability. The reliability of the emotional stability measure was poor ($\alpha = .47$).

Perceived stress was measured with four items from the 4-item Perceived Stress Scale (Cohen & Williamson, 1988). Participants were asked to rate how often stressful events occurred during the past 3 months on a scale from 0 = never to 4 = very often. Sample items include: "How often have you felt that you were unable to control the important things in your life?" and "How often have you felt difficulties were piling up so high that you could not overcome them?" Reliability of the Perceived Stress Scale was adequate ($\alpha = .68$).

Statistical analyses

Two HCC values were beyond three standard deviations from the mean, and were winsorized to three standard deviations (Ghosh & Vogt, 2012). HCC was positively skewed, and was thus log-transformed to achieve a normal distribution. Racial differences in study variables were examined using Pearson chi-square tests and independent samples t-tests. Associations among variables were analyzed using bivariate correlations.

To examine associations of race and perceived discrimination with log-HCC while controlling for potential confounding variables, hierarchical multiple regression was performed. Step 1 of the model included covariates: age, sex, annual household income, physical activity, WHR, emotional stability, and perceived stress. Race was added at step 2, and perceived discrimination was added at step 3. To determine whether the association of perceived discrimination with log-HCC differed by race, a race x discrimination interaction term was added at step 4.

Mediation analysis was performed using PROCESS (Hayes, 2013) to test whether the association between African American race and log-HCC was mediated by perceived everyday discrimination. Bootstrapping (5,000 repetitions) was used to derive 95% confidence intervals for the indirect effect, which is the product of the path from race to discrimination and the path from discrimination to log-HCC. All covariates from the moderation analysis were included in the mediation analysis. Alpha was set at .05 for all hypothesis testing. Analyses were performed using Mplus version 7.4 (Muthen & Muthen, 2015).

RESULTS

Descriptive information of the study sample is provided in Table 1. Attributions for discrimination are shown in Figure 3. African Americans reported more race-based discrimination attributions than Whites (χ^2 [1,78] = 53.43, $p < 0.001$), whereas Whites reported more age (χ^2 [1,78] = 23.00, $p < 0.001$) and physical appearance attributions (χ^2 [1,78] = 7.48, $p = 0.006$).

Bivariate correlations are shown in Table 2. Perceived everyday discrimination was associated with lower annual household income, less frequent physical activity, lower emotional stability, and with greater perceived stress. Additionally, log-HCC was positively associated with older age, African American race, and greater WHR. Perceived everyday discrimination was not associated with log-HCC ($p = 0.084$). Log-HCC was not associated with hair washing frequency ($p = 0.160$) or use of hair treatments: conditioner

(p = 0.123), bleach (p = 0.229), permanent wave (p = 0.490), and straightening (p = 0.447).

Moderation analysis

Table 3 shows the linear regression model predicting log-HCC. Covariates included in step 1 of the model explained 11.5% of the variance in log-HCC (F [7,133] = 3.03). The addition of race to the model in step 2 explained an additional 2.7% of the variance in log-HCC, and the addition of perceived discrimination in step 3 explained 2.1% of the log-HCC variance beyond step 2. The race x discrimination interaction term, added in step 4, accounted for an additional 2.6% of the variance in log-HCC beyond the step 3 model (F [1,130] = 4.35), producing a final model that explained 19% of the variance in log-HCC (F [10,130] = 3.46). Given the significant R^2 change statistic indicating that race moderated the association between perceived everyday discrimination and log-HCC, the interaction was probed to determine the association of perceived everyday discrimination with log-HCC among White and African American participants (Figure 4). Perceived everyday discrimination was positively associated with log-HCC among African American (β = 0.28, p = 0.007) but not White (β = -0.11, p = 0.274) participants, thus supporting Hypothesis 1.

Mediation analysis

When entered into a model predicting log-HCC (controlling for covariates), African American race was associated with elevated log-HCC. Upon addition to the model, perceived everyday discrimination was also positively associated with log-HCC, and the association of race with log-HCC was attenuated (Table 3, Step 3). However, African American race was not associated with perceived discrimination (β = .13, p = 0.087). The indirect effect, linking African American race to increased log-HCC via increased perceived discrimination, was not significantly different from zero ($\beta = 0.025$, 95% CI [-0.003, 0.087]), indicating that perceived discrimination did not mediate the association of African American race and log-HCC. Hypothesis 2 was thus not supported.

DISCUSSION

This study provides evidence that perceived discrimination is uniquely associated with HPA axis function in African Americans relative to Whites. Although researchers have posited the relationship between discrimination and elevated HPA axis output among groups disproportionately exposed, empirical support demonstrating an association is lacking. This study examined the association between perceived everyday discrimination and long-term retrospective cortisol levels in scalp hair among African American and White adults, finding that race moderated the association, such that perceived discrimination was positively associated with HCC among African American but not White adults. Additionally, perceived discrimination frequency did not mediate the association of African American race and elevated HCC. These results offer critical evidence supporting an association between perceived discrimination and elevated HCC in African Americans, and suggest that some aspect of discrimination other than reported frequency of occurrence (e.g., uniqueness of African American experience with discrimination), may account for observed racial differences in HCC.

The main finding of race moderating the association between perceived discrimination and HCC supports theories suggesting that discrimination may be more detrimental to the HPA axis for racial minority groups compared to majority groups (Clark et al., 1999; Myers, 2009; Williams & Mohammed, 2009). This finding is in line with prior studies showing that perceived discrimination is related to indicators of HPA axis dysregulation in the form of flattened diurnal salivary cortisol slopes (Zeiders et al.,

2014) and lower waking salivary cortisol levels (Adam et al., 2015) among African American compared to White adults. The current study provides evidence that perceived discrimination is disproportionately related to another indicator of altered HPA axis activity—elevated long-term cortisol levels—among African Americans, which are associated with adverse health indicators in this population, including elevated hemoglobin A1C, a marker of poor glycemic control (Lehrer, Dubois, Maslowsky, Laudenslager, & Steinhardt, 2016).

Although discrimination is suggested to be stressful for all individuals according to interracial stress models (Trawalter et al. 2009), there was no association of perceived discrimination with HCC among White participants in this study. In a population study of perceived discrimination and hair cortisol among primarily White adults, reported discrimination due to age, sex, and weight were all positively associated with HCC (Jackson & Steptoe, 2018). In that study, participants were classified as yes if they regularly reported discrimination in any of the above three domains and no if they did not, allowing for comparison of high vs. low perceived discrimination. Age-, gender-, and weight-based discrimination were common forms of discrimination reported by White participants in the current study, but the sample was not sufficiently powered to examine associations of HCC with these specific types of discrimination or dichotomize participants into high vs low discrimination on specific attribution domains.

It is important to note that due to the legacy of slavery and systemic racism in the U.S., African Americans are disproportionately exposed to ongoing experiences of discrimination and unfair treatment across the life course (Reskin, 2012). Consequently, exposure to discrimination is chronic, shaping health risks across generations and starting as early as in-utero (Goosby, Cheadle, & Mitchell, 2018). For example, Kuzawa and Sweet (2009) argue that exposure of African American women to discrimination can not only shape their own HPA axis function, but can also prepare their offspring in anticipation of similar discriminatory environments through epigenetic processes linked to in-utero exposure to elevated cortisol levels. Race differences in HPA function between African American and White infants can be seen as early as one year with differences partially explained by maternal exposure to discrimination (Dismukes et al., 2018). This suggests a unique social experience for African Americans that distinguishes their risk for HPA axis upregulation in a way that does not impact Whites.

The present study's finding of racial differences characterizing the association between everyday discrimination and HCC add to the emerging discrimination and hair cortisol literature. In previous work, lifetime discrimination was positively associated with HCC in a racially diverse sample of young adults (O'Brien et al., 2017). No moderation by race was found, possibly due to the lifetime discrimination scale assessing *major past discrimination events* involving *socioeconomic restriction* (e.g., being denied a loan or college admission), while the Everyday Discrimination Scale used in the present study measures *day-to-day occurrences of unfair treatment*. Restricting socioeconomic advancement may be detrimental regardless of race, while perceptions of unfair treatment may be more salient to racial minority individuals, supporting the positive association between everyday discrimination and HCC only for African Americans in the present study.

This study's secondary hypothesis was that perceived discrimination would partially mediate the association of African American race and HCC, such that African American race would be positively associated with HCC via increased perceived discrimination. Although African American race and perceived discrimination were both positively associated with HCC (steps 2 and 3 of regression model in Table 3), this hypothesis was not supported, largely because African American and White participants reported similar levels of perceived everyday discrimination. It is not clear why both groups reported similar discrimination scores, given that African Americans generally report more frequent discrimination than Whites (Kessler et al., 1999; Sternthal et al., 2011). Considerably more Whites reported age- and physical appearance-based discrimination compared to African Americans, which likely contributed to the higher than expected perceived discrimination scores among Whites. Regardless of why perceived discrimination scores were similar, it remains that racial differences in HCC were not explained by differences in perceived discrimination frequency in this study.

African American participants reported considerably more race-based discrimination than did Whites, so the attribution for discrimination (i.e., race-based vs other discrimination types) may be particularly important for HPA axis function. In past research, racial discrimination was associated with greater psychological distress than non-racial discrimination among African Americans (Chae, Lincoln, & Jackson, 2011). Further, African American women attributing mistreatment to race had higher blood pressure reactivity than those attributing mistreatment to other factors (Guyll, Matthews, & Bromberger, 2001). Because most participants in the present study reporting race-based discrimination were African American, it is reasonable to assume that racial discrimination is a highly salient form of discrimination for African Americans that may account for differences in HPA axis function.

African American populations display elevated HCC relative to other racial groups, which has been attributed in part to slower hair growth rate allowing greater cortisol accumulation in hair (Wosu et al., 2015). We similarly found higher HCC in African Americans than Whites, although we did not measure hair growth rate, which is a limitation of the present study. This difference in HCC did not likely affect the finding of race moderating the association between everyday discrimination and HCC, because

African Americans had comparable HCC to Whites at lower discrimination levels (Figure 4). However, most participants reporting race-based attributions were African American and most reporting other attributions were White (Figure 3), so the observed difference in HCC by attribution was possibly influenced by different hair growth rates of African Americans versus Whites. As our study was underpowered to compare HCC between African Americans reporting race-based attributions and African Americans reporting other attributions, future work should investigate this question in a larger sample to better probe the influence of race-based discrimination on elevated HCC among African Americans.

In addition to not assessing hair growth rate, there were several study limitations. Given the cross-sectional design, temporal associations between discrimination and HCC were not determined. Because participants possibly experienced discrimination for longer than they reported, prior discrimination exposure could influence HCC. Prospective studies could investigate how chronic discrimination longitudinally influences HCC. In addition, our study did not account for anticipatory stress and vigilance which are possible pathways through which discrimination impacts HPA axis function. To maximize efficiency, the HPA axis adjusts its activity based on immediate, continuing, and predicted forthcoming adversity, and in the presence of a chronic stressor, the HPA axis upregulates in response (Sterling, 2004). For African Americans, discrimination experiences are chronic stressors experienced and anticipated both emotionally and physiologically (Goosby, Straley, & Cheadle, 2017), and anticipation of racial discrimination is associated with metabolic and cardiovascular risk factors (Clark, Benkert, & Flack, 2006; Hicken, Lee, Ailshire, Burgard, & Williams, 2013; Powell, Jesdale, & Lemon, 2016). Thus, future research should assess anticipatory stress and vigilance related to discrimination in addition to discrimination experiences.

Future research should also integrate the various time scales through which HPA-axis responds to stress exposure. HCC does not capture HPA axis dynamics (e.g., amplitude/duration of cortisol response to stress, diurnal cortisol patterns). Thus, it is unknown whether elevated HCC for African Americans reporting high discrimination reflects increased responsiveness to daily stressors (e.g., discrimination), higher baseline cortisol, or both. Further research should characterize this upregulation.

The study sample was primarily low-socioeconomic status (SES), which may limit generalizability to higher-SES individuals. A growing literature suggests that at higher SES, African Americans still have poorer health profiles relative to Whites, with the difference partially explained by higher rates of interpersonal discrimination (Colen, Ramey, Cooksey, & Williams, 2018; Howard & Sparks, 2015) for which higher SES African Americans report more of relative to their lower SES counterparts (NPR et al., 2017). Research assessing cortisol output demonstrates that SES can moderate the relationship between discrimination and cortisol output (Fuller-Rowell et al., 2012) and minority individuals reporting low and high SES had higher HCC than those reporting moderate SES (O’Brien, Tronick, & Moore, 2013). However, this evidence is limited, and more diverse and larger study samples are required to more clearly assess these relationships. Despite these limitations, this study suggests that perceived discrimination is associated with elevated HPA axis output among African American but not White adults.

Table 1. Descriptive information of the study sample

	Full Sample (N = 141)	White (n = 72)	African American (n = 69)	*t* or χ^2
Age, years	45.77 (15.17)	42.35 (15.04)	49.33 (14.58)	-2.80**
Sex, n female (%)	95 (67)	41 (57)	54 (78)	7.28**
Annual household income, n ≥ $40,000/year (%)	77 (55)	48 (67)	29 (42)	8.63**
Hair washes/week	3.10 (2.27)	4.60 (2.01)	1.54 (1.24)	10.91***
Hair Treatment Use				
Conditioner, n yes (%)	112 (79)	51 (71)	61 (88)	6.66*
Bleach, n yes (%)	19 (14)	8 (11)	11 (16)	0.71
Permanent Wave, n yes (%)	23 (16)	1 (1)	22 (32)	24.00***
Straightening, n yes (%)	34 (24)	5 (7)	29 (42)	24.70***
Days of ≥ 30 min physical activity/week	3.48 (2.09)	4.13 (1.92)	2.81 (2.06)	3.92***
Waist to hip ratio	0.88 (0.09)	0.87 (0.08)	0.89 (0.09)	-1.33
Emotional stability	5.20 (1.32)	5.20 (1.21)	5.19 (1.43)	0.06
Perceived stress	1.21 (0.72)	1.17 (0.71)	1.26 (0.75)	-0.80
Perceived everyday discrimination	10.06 (4.38)	9.54 (3.22)	10.61 (5.29)	-1.44
Hair cortisol concentration, pg/mg, median (IQR)	7.7 (16.6)	6.0 (7.2)	8.6 (21.2)	-2.27*

Note. All data provided as mean (standard deviation) unless indicated otherwise. Group comparisons were performed using *t*-tests for continuous variables and Pearson chi-square tests for categorical variables. IQR = interquartile range. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

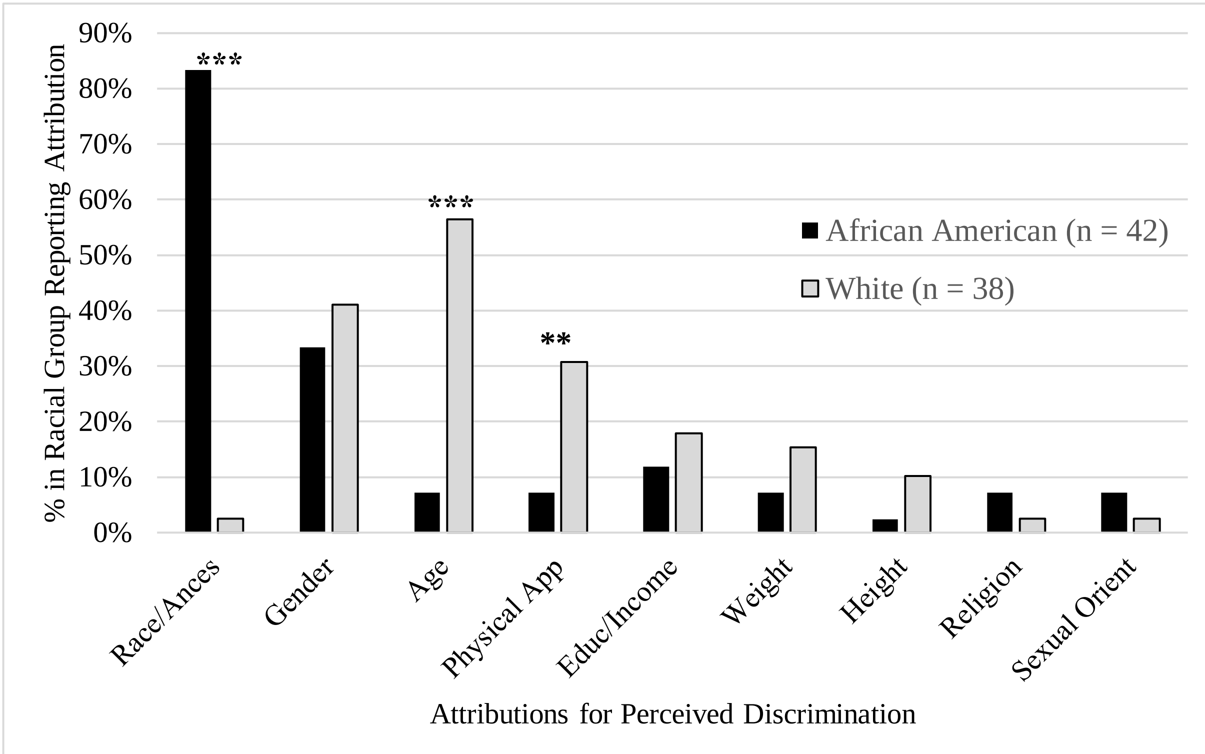

Figure 3. Bar graphs depicting the distribution of perceived discrimination attributions by race. Race/Ances = Race/Ancestry; Physical App = Physical Appearance; Educ/Income = Education/Income; Sexual Orient = Sexual Orientation. ** $p < 0.01$; *** $p < 0.001$.

Table 2. Bivariate correlations among variables involved in inferential analyses (N = 141).

	1	2	3	4	5	6	7	8	9
1. Age	-								
2. Sex	.17*	-							
3. Race	.23**	.23*	-						
4. Annual Household Income	.22*	-.05	-.24**	-					
5. Physical Activity	-.13	-.09	-.32***	.15	-				
6. WHR	.36***	-.24**	.11	-.08	-.09	-			
7. Emotional Stability	.03	-.07	.00	.25**	.16	.02	-		
8. Perceived Stress	-.13	.04	.07	-.29***	-.15	.03	-.38***	-	
9. Perceived Discrimination	-.12	-.06	.12	-.21*	-.20*	.01	-.31**	.45***	-
10. Log-HCC	.20*	-.07	.19*	-.11	.07	.25**	-.04	.05	.15

Note. Sex (Male = 0, Female = 1); Race (White = 0, African American = 1). WHR = Waist to hip ratio; HCC = Hair cortisol concentration. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 3. Standardized coefficients from regression models predicting log-hair cortisol concentration (N = 141).

	Step 1		Step 2		Step 3		Step 4	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Age	0.21^{*}	0.024	$0.17^{\dagger}$	0.073	$0.18^{\dagger}$	0.051	$0.15^{\dagger}$	0.097
Sex	-0.07	0.448	-0.10	0.256	-0.08	0.360	-0.03	0.781
Annual Household Income	-0.15	0.069	-0.10	0.246	-0.09	0.254	-0.09	0.275
Physical Activity	0.14	0.113	0.19*	0.040	0.20*	0.020	0.19*	0.029
WHR	$0.16^{\dagger}$	0.052	$0.16^{\dagger}$	0.059	$0.16^{\dagger}$	0.053	0.21**	0.009
Emotional Stability	-0.03	0.774	-0.05	0.604	-0.02	0.823	0.01	0.907
Perceived Stress	0.04	0.693	0.04	0.704	-0.02	0.817	-0.01	0.898
Race			0.19^{*}	0.030	$0.17^{\dagger}$	0.054	$-0.29^{\dagger}$	0.172
Perceived Discrimination					0.17*	0.045	-0.11	0.283
Race x Discrimination							0.59**	0.007
Model R^2	0.115		0.142		0.163		0.189	
F for R^2 Change	3.03*	0.022	4.22*	0.030	3.20*	0.045	4.35**	0.007

Note. Sex (Male = 0, Female = 1); Race (White = 0, African American = 1). WHR = waist to hip ratio.
† $p < 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < .001$.

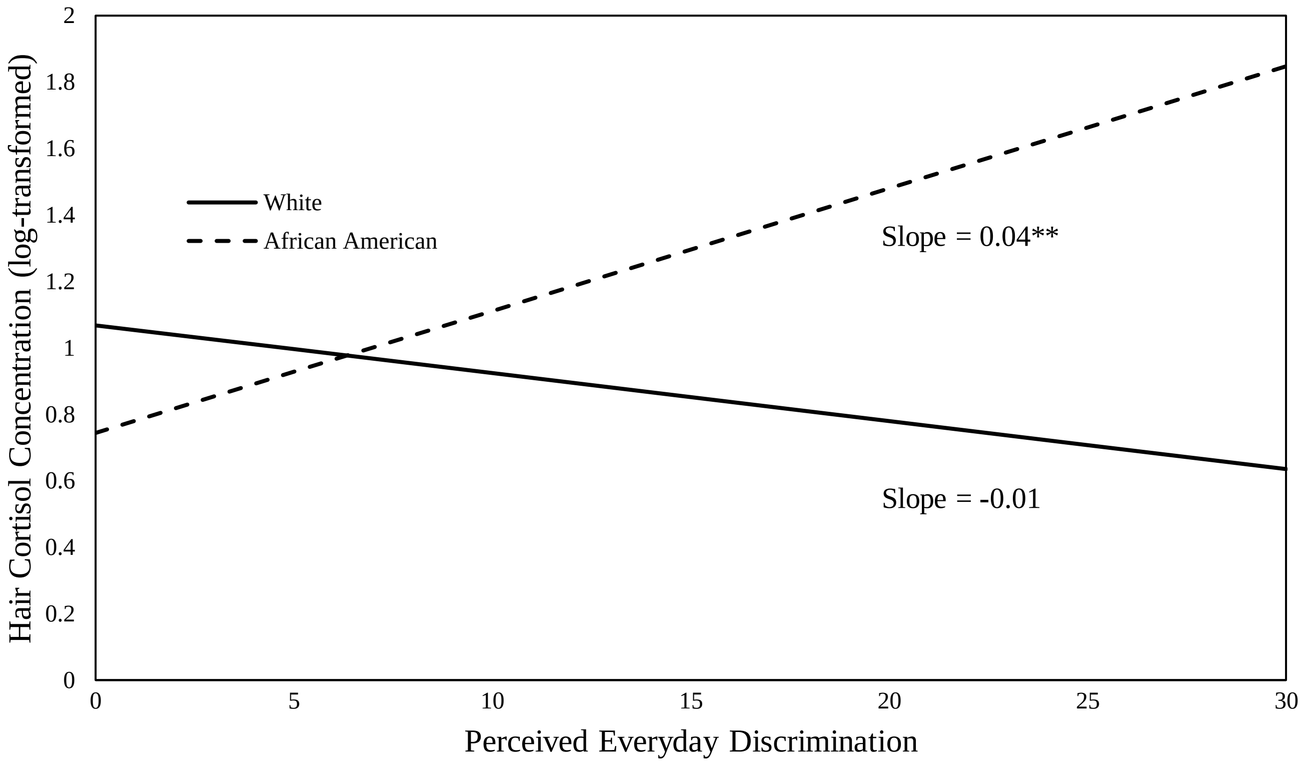

Figure 4. Simple slopes depicting the association between perceived everyday discrimination and hair cortisol concentration for White and African American participants. N = 141. ** $p < 0.01$.

Chapter 3: Study 2 – Perceived Stress, Resilience, Hair Cortisol Concentration, and Metabolic Syndrome Severity: A Moderated Mediation Model

ABSTRACT

Psychological resilience is considered to protect against detrimental effects of perceived stress on cardiovascular and metabolic health, but few studies have tested biological mechanisms underlying these relationships. The purpose of this study was to examine whether resilience moderated the indirect association of perceived stress with Metabolic Syndrome (MetS) severity via hair cortisol concentration (HCC), a retrospective index of hypothalamic pituitary adrenal (HPA) axis activity. Participants included 228 adults (73 White, 86 Hispanic, 69 African American; mean age 45.29 years; 68% females). Participants completed questionnaires assessing perceived stress and resilience. The first 3 cm of scalp-near hair were analyzed for cortisol concentration using enzyme-linked immunoassay analysis. Cardiometabolic risk factors including blood glucose, lipids, blood pressure, and waist and hip circumference were assessed, from which a sex- and race/ethnic-specific continuous MetS severity score was calculated. A moderated mediation model was tested using path analysis. Resilience moderated the association of perceived stress with HCC (R^2 change for interaction = 0.014, p = 0.042), such that the association of perceived stress and HCC weakened as resilience scores increased. Resilience also moderated the indirect association of perceived stress with MetS severity via HCC (β = -0.019, 95% CI [-0.002; -0.054]), such that HCC mediated the association of greater perceived stress with greater MetS severity only for individuals reporting resilience scores less than 1 standard deviation below the mean. Resilience was also directly associated with lower MetS severity (β = -0.224, p = 0.012) independent of

perceived stress and HCC. Findings support the role of resilience as both a stress buffer and as a direct determinant of cardiometabolic health, and extend literature on resilience to measures of retrospective HPA axis function and MetS severity in a diverse sample.

INTRODUCTION

The Metabolic Syndrome (MetS) is an increasingly prevalent clustering of cardiometabolic disease risk factors, and includes central adiposity, hypertension, hyperglycemia, and dyslipidemia. As an indicator of multisystem physiological dysregulation, MetS is a predictive diagnostic condition and the gateway to type 2 diabetes (T2D), cardiovascular disease (CVD), and stroke (O'Neill & O'Driscoll, 2015). Over 1/3 of the United States (U.S.) adult population has MetS according to standard criteria, and the 35% increased prevalence from 1988 to 2012 shows that MetS is rising rapidly (Moore, Chaudhary, & Akinyemiju, 2017).

Perceived stress, defined as "feelings or thoughts an individual has about how much stress they are under over a given period" (Phillips, 2013), is a modifiable MetS determinant (Bergmann, Gyntelberg, & Faber, 2014). Individuals reporting elevated perceived stress have increased risk of coronary heart disease (Richardson et al., 2012), stroke, myocardial infarction, and death due to CVD (Cummings et al., 2016). Perceived stress is positively associated with MetS using various criteria (Cardel et al., 2017; Raikkonen, Matthews, & Kuller, 2007), even after accounting for physical activity, nutrition, smoking status, and alcohol intake.

According to the allostatic load model, the hypothalamic pituitary adrenal (HPA) axis is the primary biological pathway by which perceived stress influences cardiovascular and metabolic processes (McEwen, 1998). The hypothalamus senses threat from the amygdala and secretes corticotropin releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH), signaling the adrenal cortex to produce cortisol. Cortisol directs target tissues to mobilize resources to address the threat, promoting gluconeogenesis and glycogenolysis to elevate blood glucose (Rosmond, 2005), and proteolysis and lipolysis to increase circulating amino acids and free fatty acids. Cortisol also increases heart rate and blood pressure (Brotman et al., 2007), and directs adipocyte proliferation and transport from peripheral to central stores (Lee et al., 2014).

When engaged chronically, these cortisol-induced cardiometabolic responses may impair health. A flatter decline in cortisol secretion across the day (indicative of a malfunctioning HPA axis and greater overall cortisol exposure) is associated with elevated glucose, LDL and total cholesterol, triglycerides, blood pressure, waist circumference, and CVD risk (Corbalán-Tutau, Madrid, Nicolás, & Garaulet, 2014; Kumari, Shipley, Stafford, & Kivimaki, 2011), and predicts impaired fasting glucose and incident T2D (Hackett, Kivimäki, Kumari, & Steptoe, 2016). Additionally, all MetS symptoms occur in pathological, endogenous hypercortisolism (Cushing's Syndrome), and most of these features subside when excess cortisol is removed (Walker, 2006). Thus, evidence supports an association between altered HPA axis function and clinical manifestations resembling MetS.

However, past studies of cortisol concentration and MetS prevalence have been inconsistent, demonstrating positive associations (Abraham, Rubino, Sinaii, Ramsey, & Nieman, 2013; Phillips et al., 2010) and no associations (DeSantis et al., 2011; Kidambi et al., 2007), possibly due to measurement challenges characterizing both cortisol and MetS. Most studies investigating the cortisol-MetS relationship obtain circulating cortisol levels *at time of sampling* (e.g., saliva, blood), which are sensitive to assessment conditions (e.g., circadian rhythmicity, psychological stress due to collection procedures). MetS development is more likely affected by *longer-term* cortisol elevation (Walker, 2006), which can be best captured in hair analyses.

Capitalizing on the continuous incorporation of hormones into growing hair, the analysis of cortisol in scalp hair is a valid (Thomson et al., 2010) and reliable (Stalder et al., 2012) indicator of retrospective HPA axis function over several months. Hair cortisol concentration (HCC) is positively associated with MetS prevalence (Kuehl et al., 2015; Stalder et al., 2013), and with BMI and waist circumference in a large, population-based cohort (Jackson, Kirschbaum, & Steptoe, 2017). A meta-analysis revealed consistent positive associations of HCC with BMI, waist-to-hip ratio, and systolic blood pressure (Stalder et al., 2017). These studies show consistent, expected associations of HCC with MetS and its components, although this work is mostly limited to White samples.

In addition to the advancement in cortisol assessment provided by hair analysis, MetS measurement has also progressed. The binary nature of traditional MetS likely contributes to racial/ethnic MetS discrepancies (e.g., lower MetS rates for Hispanic and African American adults despite elevated CVD and T2D prevalence) (Moore et al., 2017; Ukegbu et al., 2011), as it requires extreme thresholds inappropriate for all groups, particularly groups with generally lower values of MetS components (e.g., lower triglyceride levels among African American adults) (Sumner, 2009). Binary MetS classification also prevents tracking a condition over time—an important drawback given that MetS is a diagnostic tool widely used in clinical settings. A recently-developed continuous MetS severity score overcomes these issues by weighting individual MetS components by how they correlate together as a manifestation of the physiological processes underlying MetS, accounting for sex and race/ethnicity variation in that weighting (Gurka et al., 2014). In nationally-representative samples, the MetS severity score was positively associated with insulin resistance (Gurka et al., 2014) and predicted coronary heart disease (DeBoer et al., 2017) and incident T2D (Gurka et al., 2017) beyond variance explained by individual MetS components. Importantly, in a sample with T2D expected to have high MetS prevalence, inaccurate racial/ethnic differences in MetS (i.e., African American men having lower MetS prevalence compared to White and

Hispanic men) disappeared when implementing the MetS severity score (Gurka et al., 2014). The MetS severity score is a valid, continuous index of MetS that may be especially useful in diverse populations.

The association of perceived stress with MetS severity via HPA axis function may depend on an individual's resilience, defined as "the ability to bounce back or recover from stress" (Smith et al., 2008). Individuals with low resilience have compromised control of brain circuits involved in emotion and fear (Southwick & Charney, 2012), and poor cortico-limbic inhibition, representing a dysregulated emotional response to stress that may result in elevated cortisol exposure (Gupta et al., 2017). To date, there has been little consideration of the interplay between perceived stress and resilience in relation to HCC, although studies have examined this interaction in relation to salivary cortisol. High-resilience caregivers of individuals with Autism displayed a lower salivary cortisol output following an acute stressor, indicating lower levels of overall cortisol exposure (Ruiz-Robledillo, Romero-Martínez, & Moya-Albiol, 2017). When challenged with a laboratory stressor, high-resilience men secreted less cortisol than low-resilience men in anticipation of a stressor (Mikolajczak, Roy, Luminet, & de Timary, 2008). Given the protective effect of resilience on the relationship between perceived stress and salivary cortisol, we expect that higher resilience will similarly buffer the association of perceived stress with HCC.

In addition to the ability of resilience to moderate the association of perceived stress with cortisol, resilience may also directly benefit cardiometabolic health. Low resilience was associated with an increased risk of T2D development in a study of 1.5 million adults followed up for an average of 26 years (Crump, Sundquist, Winkleby, & Sundquist, 2016), and with worsening A1C over 1 year follow-up among individuals with diabetes (Yi, Vitaliano, Smith, Yi, & Weinger, 2008). Resilience was also negatively associated with BMI and waist circumference among men (Stewart-Knox et al., 2012). Individuals' cardiometabolic health may thus directly benefit from high levels of resilience, regardless of a stress-buffering effect.

The purpose of this study was to examine whether resilience moderated the indirect association of perceived stress with MetS severity via HCC. The hypotheses were: 1) Resilience will moderate the indirect association of greater perceived stress with greater MetS severity via elevated HCC, such that higher levels of resilience will be associated with an attenuated indirect association, and 2) Greater resilience will be associated with lower MetS severity independent of an interaction with perceived stress.

METHODS

Participants and Procedures

Participants were 228 community-dwelling adults (73 White, 86 Hispanic, 69 African American; mean age 45.29 years; 68% females) recruited through word of mouth, flyers posted on campus and at neighborhood establishments, and on an online University research board. Exclusion criteria were baldness or shaved head, pregnant or lactating, use of glucocorticoid-containing medication, and diagnosed type 1 diabetes. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of the sponsoring university. Participants were compensated $20 for their time.

All study variables for each participant were assessed during a single study visit. Demographic and psychosocial measures were collected via brief questionnaire. Hair samples for cortisol analysis were collected primarily by a trained hair stylist, and the remainder were taken by a trained research staff member if data collection scheduling conflicts for participants arose. Blood samples for lipids and glucose were taken via finger prick. Waist/hip circumference and blood pressure were measured by trained research staff.

Measures

Medication and Lifestyle Characteristics

Medication use, hair care practices, and physical activity were assessed. Medication use was established by asking participants to list their prescription medications over the prior three months and the reason for taking each medication. Use of medicines for blood pressure, diabetes, and cholesterol are reported. To assess overall medication use, participants received a 1 for each category of medication they used, and a sum score (ranging from 0-3) was calculated as total medication use. The assessment of hair related characteristics included the number of hair washes per week (0-7) and the use of hair treatments (e.g., conditioner, bleach) during the past three months. Hair washing frequency and hair treatments are often associated with slightly lower HCC values, according to a recent meta-analysis (Stalder et al., 2017). Participants answered yes or no to each of the following: conditioner, bleach, permanent wave, and straightening. Physical activity was assessed with the item: "How many days per week do you perform at least 30 minutes of physical activity?" Responses ranged from 0 to 7.

Annual Household Income

Annual household income was assessed by asking participants to: "Please select your family's current yearly income before taxes." Answers ranged from 1 *($19,999 or less*) to 6 (*$100,000 or more*), and increased in $20,000 intervals.

Psychosocial Variables

Perceived Stress was measured using the 4-item Perceived Stress Scale (PSS-4) (Cohen et al., 1983), which measures the appraised stressfulness of the respondent's life situations during the past 3 months on a scale from 0 (*never*) to 4 (*very often*). Sample items included: "How often have you felt that you were unable to control the important things in your life?" and "How often have you felt difficulties were piling up so high that you could not overcome them?" The PSS-4 score was calculated as the average of the 4 items. The reliability of the PSS-4 was adequate ($\alpha = 0.64$).

Resilience was assessed with the 6-item Brief Resilience Scale (BRS) (Smith et al., 2008), which measures respondents' ability to bounce back from stress on a scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). Sample statements included: "I tend to bounce back quickly after hard times," "It does not take me long to recover from a stressful event," and "I usually come through difficult times with little trouble." The BRS score was calculated as the average of the 6 items. The reliability of the BRS was acceptable ($\alpha = 0.77$).

Emotional Stability was measured with a two-item subscale from the Big 5 Personality Inventory Short Form (Rammstedt & John, 2007). Participants were asked "How well do the following statements describe your personality?" Stemmed by, "I see myself as someone who…," the responses were: "is relaxed, handles stress well," and "gets nervous easily." Responses ranged from 1 (*disagree strongly*) to 7 (*agree strongly*). The second response was reverse coded and the scores summed, so that higher scores indicate greater emotional stability. The reliability of the emotional stability subscale was poor ($\alpha = 0.46$).

Hair Cortisol Assessment

Hair was cut by a professional hair stylist using thinning shears close to the scalp at the posterior vertex. Hair length was measured after stretching to full length and the proximal 3 cm was ground and analyzed as previously described (Russell et al., 2015). Cortisol levels were determined using a commercial high sensitivity enzyme-linked immunoassay (EIA) kit (Salimetrics LLC, State College, PA, USA) per manufacturer's protocol. Inter- and intra-assay coefficients of variation were 9.2% and 2.8%, respectively. Results are reported as pg/mg, which corrects for the weight of hair extracted.

Cardiometabolic Parameters

Non-fasting blood samples for the measurement of high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose were obtained and analyzed according to standard laboratory procedures. Specifically, HDL, triglycerides, and glucose were measured enzymatically with Alere reagent on a Cholestech LDX analyzer (Alere, Waltham, MA). Anthropometric and blood pressure assessments were performed by trained research staff. Waist and hip circumferences were measured to the nearest 0.1 cm using a non-stretchable standard tape measure: 0.1 cm above the iliac crest on a horizontal plane and at the widest portion of the hip, respectively. Waist to hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. Systolic blood pressure was measured using an Omron HEM-907XL Automatic Inflation Blood Pressure Monitor (Omincron, Philadelphia, PA), and was calculated as the mean value of three measurements taken within a 15-minute period.

MetS Severity Score

MetS severity was calculated as a Z-score for participants using validated sex and race/ethnicity-based equations using data from adults in the National Health and Nutrition Examination Survey 1999–2010. (Gurka et al., 2014). The coefficients used in the equations were derived using a confirmatory factor analysis of a single MetS factor that allowed loadings of the traditional five MetS components to vary across sex and race/ethnicity, resulting in a sex and race/ethnicity-specific continuous MetS severity score.

Statistical Analyses

Three HCC values were above three standard deviations (SDs) from the mean, and were winsorized (i.e., replaced by the closest value within 3 SDs) as performed elsewhere (Ghosh & Vogt, 2012). The resulting distribution displayed positive skew and was thus log-transformed to achieve a normal distribution. Descriptive statistics (means, standard deviations, percentages) for all variables were calculated in the full sample and for each racial/ethnic group using SPSS version 25 (IBM, Chicago, Illinois). Bivariate correlations and moderation, mediation, and moderated mediation analyses were conducted using Mplus, version 7.4 (Muthen & Muthen, 2015). Full information maximum likelihood (FIML) estimation was used to handle missing data. FIML is a robust missing data method that uses all available data to estimate each model path while also providing unbiased standard errors, based on actual available data for a given parameter estimate rather than the total analytic sample size (Myrtveit, Stensrud, & Olsson, 2001).

Moderation

To examine the interaction of perceived stress and resilience with log-HCC while controlling for potential confounding variables, hierarchical multiple regression was performed. Step 1 of the model included age, sex (0 = male, 1 = female), race/ethnicity (Hispanic and African American as reference groups), annual household income, physical activity, emotional stability, hair washing frequency, and bleach use. To determine whether the association of perceived stress differed by resilience, a perceived stress x resilience interaction term, created from mean-centered variables, was added at step 2. A similar 2-step model was performed to examine the association of perceived stress, resilience, and log-HCC with MetS severity. Use of medications for MetS-related conditions was added as a covariate to the models predicting MetS severity.

Moderated Mediation

To determine whether resilience moderated the indirect association of perceived stress with MetS severity via log-HCC, a conditional process path model was performed in accordance with Hayes (2015). The same covariates from moderation analyses were included, as was the perceived stress x resilience interaction term. Direct and indirect effects were estimated and tested with bias-corrected 95% confidence intervals. The index of moderated mediation, computed as the product of the interaction-to-mediator path coefficient and the mediator-to-outcome path coefficient, estimated the association between resilience and the size of the indirect effect (Preacher, Rucker, & Hayes, 2007). If the index of moderated mediation significantly differed from zero, the indirect effect from perceived stress to MetS severity via log-HCC would be considered to vary as a function of resilience, indicating moderated mediation.

RESULTS

Descriptive statistics of the study sample are presented in Table 4. Additional descriptive information and breakdown by race/ethnicity is included in a supplementary table in the Appendix. Bivariate correlations among study variables are shown in Table 5. Log-HCC was positively associated with MetS severity. Resilience was negatively associated with perceived stress and MetS severity, but perceived stress was not associated with MetS severity. Neither perceived stress nor resilience were associated with log-HCC.

Table 6 shows regression results predicting log-HCC and MetS syndrome. After including covariates, neither perceived stress (b = 0.030, SE = 0.054, 95% CI [-0.068; 0.146]) nor resilience (b = 0.031, SE = 0.068, 95% CI [-0.093; 0.173]) were associated with log-HCC. However, log-HCC was positively associated with MetS severity (b = 0.347, SE = 0.126, 95% CI [0.125; 0.622]), and resilience was negatively associated with MetS severity (b = -0.344, SE = 0.138, 95% CI [-0.626; -0.085]). Although no main effects of perceived stress on log-HCC or MetS were found, testing the interaction of perceived stress and resilience on these outcomes may reveal associations that the main effects analysis did not.

Moderation

To test hypotheses that resilience moderated the association of perceived stress with log-HCC and MetS severity, a perceived stress x resilience interaction term was added in Step 2 of the models in Table 6. The interaction was associated with lower log-HCC, such that perceived stress was positively associated with log-HCC at lower levels of resilience. The perceived stress x resilience interaction was not associated with MetS severity. Figure 5 shows the association of perceived stress with log-HCC at various levels of resilience (after adjusting for covariates). For resilience scores roughly 1.4 SDs below the mean and lower, perceived stress is positively associated with log-HCC (β = 0.195). At this value of resilience, log-HCC increases roughly 0.2 SDs for each SD increase in perceived stress.

Moderated Mediation

To summarize the above results, resilience was negatively associated with MetS severity, log-HCC was positively associated with MetS severity, and resilience moderated the association of perceived stress with log-HCC. Based on these findings, a moderated mediation model was tested to examine whether the indirect association of perceived stress to MetS severity via log-HCC varied as a function of resilience (Figure 6). The index of moderated mediation was negative and significantly different from zero (β = -0.019, 95% CI [-0.002; -0.054]), indicating that the indirect association from perceived stress to MetS severity via log-HCC decreases as resilience increases (Preacher et al., 2007). As shown in Figure 7, the indirect association of perceived stress to MetS severity via log-HCC was positive for resilience scores 1 SD below the mean and lower (β = 0.026). Among low-resilience participants (1 SD below the mean and lower), higher perceived stress was associated with higher HCC, which was associated with higher MetS severity. Among high-resilience participants, this pathway was not significant.

DISCUSSION

Considered the gateway to T2D, CVD, and stroke, MetS is a rapidly-increasing clustering of risk factors with modifiable psychosocial determinants. However, factors hypothesized to influence MetS (e.g., perceived stress, resilience), and HPA axis processes posited to mediate these associations are somewhat unclear. Recent advances in HCC and MetS measurement allow for a more accurate investigation of these relationships. The present study found that resilience moderated the association between perceived stress and HCC, such that perceived stress was more strongly associated with HCC among participants with lower resilience. Further, elevated HCC mediated the association between greater perceived stress and greater MetS severity, but only for individuals with low resilience. Finally, resilience was negatively associated with MetS severity independent of an interaction with perceived stress. These findings are consistent with research characterizing resilience as both a stress buffer and as a direct benefactor of cardiovascular and metabolic health, and extend literature on how the stress-buffering effects of resilience may be transmitted via retrospective HPA axis activity in a diverse sample.

In the present study, resilience moderated the association of perceived stress with HCC. Many studies have examined associations of perceived stress with HCC, consistently producing null findings (Stalder et al., 2017). Thus, the nonsignificant association of perceived stress with HCC was not surprising in the present study, and research suggests that resilience can modify this association. Low-resilience individuals have altered control of brain circuits governing emotion and fear (Southwick & Charney, 2012) and compromised inhibition of cortico-limbic circuits, representing a distorted emotional response to stress that may result in elevated cortisol exposure (Gupta et al., 2017). When stimulated with ACTH (the precursor to cortisol in the HPA axis), low-resilience individuals have a slower recovery to baseline cortisol levels compared to high-resilience individuals (Park et al., 2018), indicating an inefficient termination of the cortisol response possibly leading to elevated cortisol levels. Resilience also moderates the relationship between a physical stressor (sleep deprivation) and serum cortisol, such that individuals with lower resilience have higher cortisol levels in response to short sleep (Sun et al., 2014). Results of the present study extend literature from the stress-buffering effects of resilience on acute measures of cortisol to a longer-term, retrospective cortisol index.

As expected, HCC was positively associated with MetS severity, although this is a novel finding among a racially/ethnically diverse sample. The bulk of HCC-MetS research has been conducted in White samples, showing anticipated associations of HCC with MetS prevalence (Kuehl et al., 2015; Stalder et al., 2013) and BMI and WHR (Jackson et al., 2017). An exception is a study finding a positive association of HCC with A1C among African American adults (Lehrer et al., 2016). Given that racial/ethnic discrepancies characterize traditional binary MetS classification, the use of a continuous sex and race/ethnicity-specific MetS severity score permitted a valid investigation into the association of HCC and MetS in the present study sample. The finding of a positive association between HCC and MetS supports the role of elevated cortisol levels in the pathophysiology of cardiometabolic disease.

The association of perceived stress with MetS severity via HCC was found to vary as a function of resilience, such that the indirect association was positive for individuals scoring 1 standard deviation below the mean on resilience and lower. A large collection of literature demonstrates the ability of resilience to protect against the detrimental effects of perceived stress on cardiovascular and metabolic health. For example, among lower socioeconomic groups, higher stress exposure compounded by lower resilience is thought to play a part in the greater susceptibility to disease observed in socioeconomic heath inequalities (Kristenson, Eriksen, Sluiter, Starke, & Ursin, 2004). Additionally, cardiovascular responses to stress can differ based on whether an individual perceives stress as challenge, versus as a threat (Seery, 2011). Low resilience has also been associated with a slower cardiovascular recovery from a stressor (Tugade & Fredrickson, 2004), representing a less adaptive termination of an individual MetS component (blood pressure) at lower levels of resilience. Further, the allostatic load model suggests that the beneficial influences of resilience on health can be transmitted via alterations in HPA axis function, which were found in the present study.

In addition to serving as a stress buffer, resilience also exhibited a direct negative association with MetS severity. Some scholars contend that resilience can only function in the context of stress (Glantz & Sloboda, 1999; Kaplan, 1999; Luthar et al., 2000), while others consider resilience to have its own benefits regardless of how much stress a person faces. One study supporting the latter showed that resilience was negatively associated with BMI and waist circumference among men (Stewart-Knox et al., 2012). Similarly, low resilience was associated with an increased risk of T2D development in a study of 1.5 million adults followed up for an average of 26 years (Crump et al., 2016), and with worsening A1C over 1 year follow-up among individuals with diabetes (Yi et al., 2008). Our findings support this body of work, and suggest resilience can be beneficial independent of an interaction with stress.

Results and interpretations of the present study should be considered in light of several limitations. First, the cross-sectional study design did not permit determination of causal effects. Given that development of more severe MetS is likely affected by long-term changes in hormone levels and vice versa, longitudinal studies are ideal to investigate how cortisol and MetS severity interact over time. Second, the psychosocial survey measures were relatively brief, which may detract from the internal consistency reliability of each measure. Cronbach's alphas for perceived stress and resilience were acceptable, while emotional stability had poor reliability, likely due to only two items for that scale. Given the questionable reliability of that measure, models were run with and without emotional stability, and results did not change appreciably. A final limitation is the use of non-fasting blood samples for glucose and lipid analyses. This limitation is partly alleviated by use of the continuous MetS severity score, which does not use threshold values of individual MetS components to classify at-risk individuals. Additionally, other research using non-fasting glucose and lipid measures reports similar ability of MetS to predict CVD and T2D compared to studies using fasting measures (Wannamethee, Shaper, Lennon, & Morris, 2005).

Despite these limitations, this study has numerous strengths, including the use of HCC as a retrospective index of HPA axis function, a racially/ethnically diverse sample, and the use of a sex and race/ethnicity-specific MetS severity score. Resilience moderated the association of perceived stress with HCC, and the indirect association of perceived stress with MetS severity via HCC, such that lower resilience was associated with a stronger association of perceived stress and HCC, and a stronger indirect association of perceived stress and MetS severity via elevated HCC. Resilience was also directly associated with lower MetS severity. These findings highlight the potentially dual benefits of resilience—as both a direct determinant and stress buffer—on cardiometabolic health.

Table 4. Descriptive information of the study sample (N = 228).

Variables	Mean (SD)
Demographic and lifestyle characteristics	
Age, years	45.29 (14.00)
Sex, n female (%)	155 (68)
Annual household income, n > $40k/yr (%)	103 (45)
Blood pressure medication, n yes (%)	38 (17)
Diabetes medication, n yes (%)	25 (11)
Cholesterol medication, n yes (%)	21 (9)
Days of $\geq$ 30 min physical activity per week	3.49 (2.12)
Psychosocial Measures	
Emotional Stability	5.09 (1.38)
Perceived Stress	1.23 (0.73)
Resilience	3.55 (0.72)
Hair-related characteristics and hair cortisol	
Hair Washes per week	4.02 (2.64)
Conditioner, n yes (%)	176 (77)
Bleach, n yes (%)	49 (22)
Hair Cortisol, pg/mg, median (IQR)	7.9 (13.5)
MetS components	
HDL cholesterol, mg/dL	52.36 (15.00)
Triglycerides, mg/dL, median (IQR)	135 (121)
Glucose, mg/dL, median (IQR)	99 (27)
WHR	0.88 (0.08)
Systolic Blood Pressure, mmHg	122.33 (16.44)
MetS Severity	0.45 (1.34)

Note. All data provided as mean (SD) unless indicated otherwise. MetS = metabolic syndrome, HDL = high-density lipoprotein, WHR = waist to hip ratio.

Table 5. Bivariate correlations among primary study variables (N = 228).

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Age														
2. Sex	0.07													
3. White	-0.14*	-0.21*												
4. Hispanic	-0.05	0.02	-0.53***											
5. African American	0.19**	0.15*	-0.45***	-0.51***										
6. Household Income	0.19**	-0.09	0.36***	-0.32***	-0.02									
7. Total Medication Use	0.41***	0.09	-0.18**	-0.09	0.28***	-0.08								
8. PA Frequency	-0.01	-0.01	0.19**	0.01	-0.21**	0.11	-0.06							
9. Emotional Stability	0.07	-0.12	0.06	-0.10	0.05	0.27***	-0.14*	0.16*						
10. Perceived Stress	-0.15*	0.06	-0.07	0.038	0.03	-0.25***	0.12	-0.12	-0.41***					
11. Resilience	0.00	-0.18**	0.09	-0.17**	0.08	0.33***	-0.13	0.18**	0.58***	-0.56***				
12. Hair Wash Frequency	-0.08	-0.32***	0.16**	0.44***	-0.62***	-0.64	-0.20**	0.14*	0.00	-0.12	0.06			
13. Bleach	0.11	0.20**	-0.27**	0.25***	-0.09	-0.11	0.01	-0.03	-0.05	0.00	-0.15*	0.01		
14. Log-HCC	0.12	-0.09	-0.14	0.03	0.12	-0.06	0.11	0.04	0.07	0.00	0.03	-0.10	0.12	
15. MetS Severity	0.27***	0.00	-0.24**	0.08	0.16*	-0.15*	0.36***	-0.15*	0.04	0.03	-0.15*	-0.09	0.05	0.25***

Note. Pearson correlations used for correlations involving one or two continuous variables. Tetrachoric correlations used for dichotomous-dichotomous correlations. Sex (Female = 1, Male = 0). Bleach (1 = Uses bleach, 0 = Does not use bleach). PA = physical activity, HCC = hair cortisol concentration, MetS = metabolic syndrome. *, *p* < .05; **, *p* < .01; ***, *p* < .001.

Table 6. Standardized coefficients from regression models predicting log-hair cortisol and MetS severity (N = 228).

	Hair Cortisol Concentration				Metabolic Syndrome Severity			
	Step 1		Step 2		Step 1		Step 2	
Variables	β	p	β	p	β	p	β	p
Age	0.104	0.123	0.105	0.114	0.119	0.103	0.118	0.107
Sex	-0.366	0.025	-0.352	0.029	-0.145	0.336	-0.146	0.336
Hispanic	0.214	0.234	0.212	0.233	0.263	0.073	0.263	0.074
African American	0.234	0.251	0.216	0.290	0.201	0.320	0.203	0.321
Annual Household Income	-0.075	0.306	-0.082	0.261	-0.092	0.183	-0.090	0.206
MetS Medication Use	-	-	-	-	0.280	<0.001	0.281	<0.001
Physical Activity Frequency	0.063	0.411	0.062	0.414	-0.122	0.045	-0.122	0.045
Emotional Stability	0.059	0.444	0.088	0.258	0.201	0.012	0.198	0.015
Hair Washing Frequency	-0.138	0.063	-0.135	0.061	-0.008	0.916	-0.008	0.916
Bleach	0.320	0.099	0.324	0.094	-0.079	0.611	-0.080	0.608
Perceived Stress	0.039	0.580	0.044	0.521	-0.077	0.218	-0.074	0.219
Resilience	0.040	0.648	0.050	0.571	-0.227	0.013	-0.228	0.014
Perceived Stress x Resilience	-	-	-0.125	0.042	-	-	0.012	0.859
Log-HCC	-	-	-	-	0.177	0.004	0.177	0.004
Model R^2	0.085		0.099		0.271		0.270	
F for R^2	2.073	0.038	-	-	5.159	<0.001	-	-
F for R^2 change	-	-	2.326	0.042	-	-	0.172	0.870

Note. Sex (Male = 0, Female = 1). Hispanic (Hispanic = 1, African American = 0, White = 0); African American (African American = 1, Hispanic = 0, White = 0). HCC = hair cortisol concentration, MetS = Metabolic Syndrome.

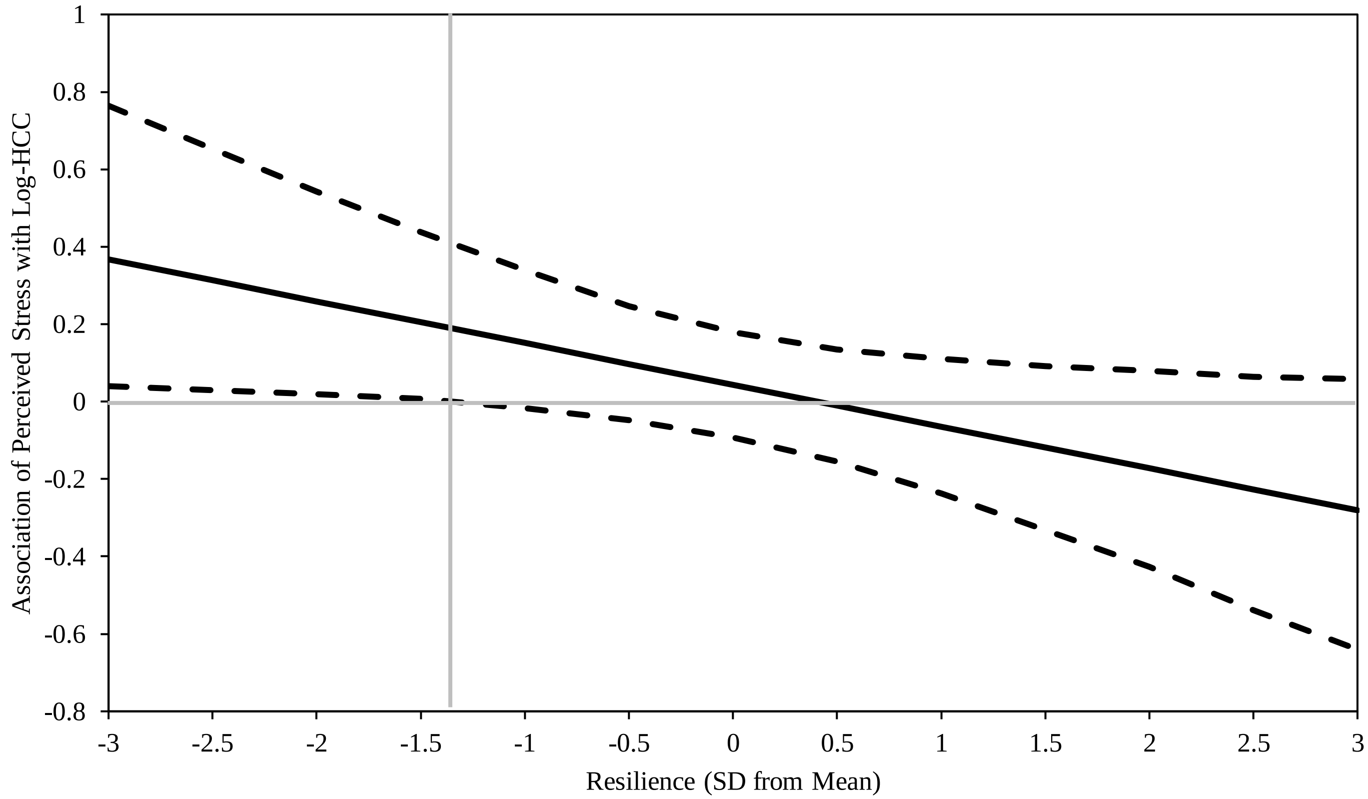

Figure 5. Confidence band for the association of perceived stress with log-HCC for different values of resilience (standardized). Dashed lines indicate the lower and upper bounds of the 95% confidence interval. The association of perceived stress and log-HCC is significantly different from zero at resilience scores 1.4 SDs below the mean and lower. HCC = hair cortisol concentration, SD = standard deviation.

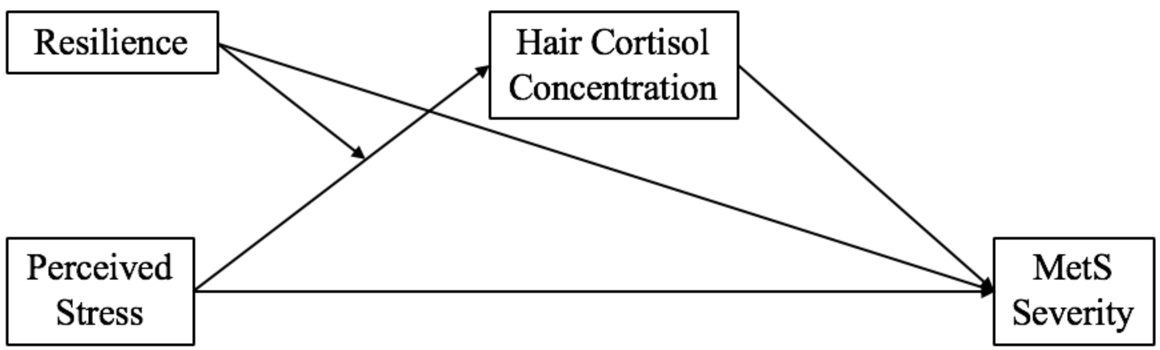

Figure 6. The conceptual moderated mediation model which was tested.

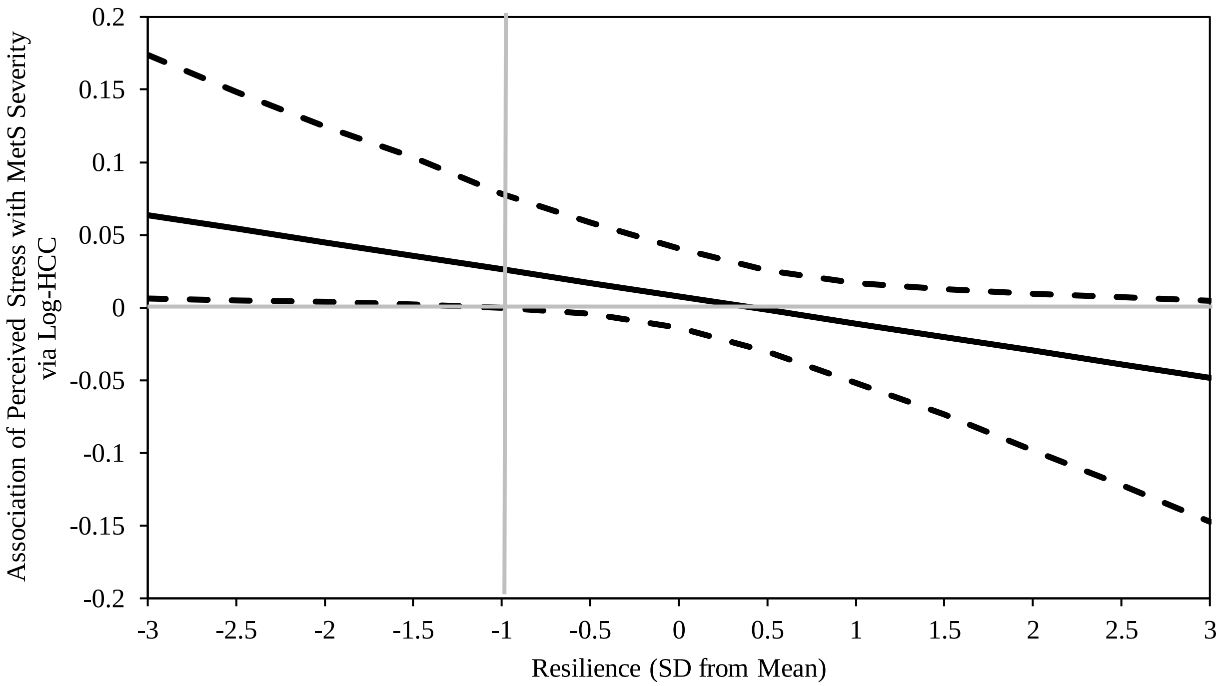

Figure 7. Confidence band for the indirect association of perceived stress with MetS severity via log-HCC for different values of resilience (standardized). Dashed lines indicate the lower and upper bounds of the 95% confidence interval. The indirect association of perceived stress with MetS severity via HCC is significantly different from zero at resilience scores 1 SD below the mean and lower. MetS = metabolic syndrome, HCC = hair cortisol concentration, SD = standard deviation.

Chapter 4: Study 3 – Longitudinal Associations of Daily Stressor Frequency and Severity with Diurnal Cortisol Slopes and Cardiometabolic Conditions

ABSTRACT

The unique roles that daily stressor frequency and severity play in the contribution to cardiovascular and metabolic disease are poorly understood, as are the interaction of these stressor characteristics with potentially beneficial psychosocial attributes in the context of cardiometabolic health. The purpose of this study was to examine prospective associations of daily stressor frequency and severity with prevalence of cardiometabolic health conditions, along with potential mediating and moderating influences of diurnal cortisol slopes and psychosocial resilience resources. Participants (N = 1,333) from the Midlife in the United States (MIDUS) study completed questionnaires at MIDUS 2 (2004-2005) assessing cardiometabolic conditions (heart disease, stroke, hypertension, type 2 diabetes, hypercholesterolemia, and obesity) and resilience resources (optimism, self-esteem, social integration, purpose in life, positive reappraisal). Participants then completed a daily diary (2004-2009) in which they reported stressors and perceived stressor severity each day for eight consecutive days, and provided saliva samples for cortisol analysis on days 2-5. At MIDUS 3, participants completed another questionnaire assessing cardiometabolic conditions (2013-2015). Structural equation modeling estimated effects of stressor frequency and severity on diurnal cortisol slopes and MIDUS 3 cardiometabolic conditions sum score, and the moderating effect of resilience resources on those associations. Greater daily stressor severity and flattened cortisol slopes were associated with greater prevalence of cardiometabolic conditions at MIDUS 3. Resilience

resources did not moderate any associations of daily stressor frequency or severity with cortisol slopes or MIDUS 3 cardiometabolic conditions. Stressor severity—rather than frequency of stressor occurrence—may be associated with risk for cardiovascular and metabolic disease later in life, independent of behavioral and psychosocial risk factors.

INTRODUCTION

Cardiovascular (e.g., heart disease, hypertension, and stroke) and metabolic (e.g., diabetes, hypercholesterolemia, obesity) diseases account for over 30% of deaths and over $500 billion in annual healthcare costs in the United States (U.S) (American Diabetes Association, 2018; Benjamin et al., 2017; Heron, 2018; Kim and Basu, 2016). Cardiovascular diseases remain alarmingly prevalent, as half of middle-aged men and one-third of middle-aged women will develop some manifestation of cardiovascular disease in their lifetime (Sanchis-Gomar, Perez-Quilis, Leischik, & Lucia, 2016). Perhaps more troublesome are the rising rates of metabolic disease: Obesity prevalence increased from 34% in 2008 to 40% in 2016 (Hales, Fryar, Carroll, Freedman, & Ogden, 2018), while type 2 diabetes prevalence has been steadily increasing for decades (Centers for Disease Control and Prevention, 2017), and is expected to reach 25% by 2050 (Boyle, Thompson, Gregg, Barker, & Williamson, 2010). Psychosocial stress is a risk factor for cardiometabolic diseases (Hackett & Steptoe, 2017; Steptoe & Kivimäki, 2012), but more research is needed to disentangle the contribution of various stressor characteristics (e.g., exposure, severity) to the development of cardiometabolic conditions, neurobiological mechanisms mediating these effects, and intra- and inter-personal resources that may protect against the influence of stress on cardiometabolic disease. Experiences and perceptions of *chronic* stress have received the bulk of research attention to date (Cohen et al., 2012; Juster, McEwen, & Lupien, 2010), but the impact of *daily* stress experiences on cardiometabolic health is a promising avenue of inquiry.

A growing body of evidence links exposure to daily stressors with cardiometabolic health. Daily stressors, or daily hassles, are tangible, relatively minor (compared to major life events such as job loss or death of a loved one), interruptions of day-to-day living such as work deadlines, family arguments, or a malfunctioning computer (Almeida, 2005). The sporadic nature of these stressors distinguishes them from recurrent chronic stressors such as those associated with work overload or being a caregiver. Increased daily stress exposure is associated with altered functioning of biological systems that contribute to cardiometabolic disease, including elevated blood pressure (Uchino, Berg, Smith, Pearce, & Skinner, 2006) and proinflammatory cytokine levels (Chiang, Eisenberger, Seeman, & Taylor, 2012). Increased reported daily hassles over two years were associated with development of cardiovascular disease risk factors over the same time period in a study of young adults (Twisk, Snel, Kemper, & van Mechelen, 1999), and individuals reporting more negative social interactions in daily life had increased risk of metabolic syndrome two years later (Ross, Martin, Chen, & Miller, 2011). Elevated exposure to daily stressors appears associated with indicators of poor cardiometabolic health, but the extent to which the perceived severity of daily stressors influences the development of adverse health outcomes over time remains to be seen.

Stressor severity, the degree to which a given event is considered stressful, is associated with reduced wellbeing and with adverse physical health symptoms. Individuals experiencing more severe stressors have been shown to have worse mental health outcomes compared to those who generally report less severe stressors (Stawski, Sliwinski, Almeida, & Smyth, 2008). Similarly, individuals reporting a greater proportion of high-severity stressors reported more physical illness symptoms (e.g., gastrointestinal discomfort and chest pain) compared to individuals who report fewer sever stressors (Grzywacz, Almeida, Neupert, & Ettner, 2004). Despite these findings, there is little research investigating associations of stressor severity with physical health outcomes, including cardiovascular and metabolic diseases.

Stress-induced perceptions of threat can modify cardiac, vascular, endocrine, and metabolic functioning (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Lovallo & Gerin, 2003; Pressman & Cohen, 2005). Repeated and prolonged activation of these systems over time can ultimately lead to development of cardiometabolic disease (McEwen and Seeman, 1999). Experiencing increased frequency and severity of daily stressors are both postulated to influence cardiometabolic disease development via dysregulated hypothalamic pituitary adrenal (HPA) axis function. The steroid hormone cortisol is the end product of the HPA axis, a neuroendocrine system that coordinates biological responses to stress (Tsigos & Chrousos, 2002). Cortisol secretion follows a diurnal pattern, with high levels upon wake-up that steadily decline throughout the day. Exposure to stress modulates the circadian activity of cortisol, being associated with a flattened cortisol decline (or slope) throughout the day (Miller et al., 2007). Flattened cortisol slopes have been associated with elevated blood glucose, LDL and total cholesterol, triglycerides, systolic and diastolic blood pressure, waist circumference (Corbalán-Tutau et al., 2014), cardiovascular disease (Matthews, Schwartz, Cohen, & Seeman, 2006), and type 2 diabetes risk (Schoorlemmer, Peeters, Schoor, & Lips, 2009).

Increased reported daily stressor frequency has previously been associated with flattened diurnal cortisol slopes in daily diary studies (Barker, Greenberg, Seltzer, & Almeida, 2012; Smyth et al., 1998; van Eck, Berkhof, Nicolson, & Sulon, 1996). However, one daily diary study found increased daily stressor frequency associated with steeper diurnal cortisol slopes. The authors suggested that increased daily stressor exposure may reflect a more social and engaged lifestyle, which is associated with health benefits (Stawski, Cichy, Piazza, & Almeida, 2013). In addition, these individuals may also possess other adaptive psychological and social attributes that confer resilience to stress.

The impact of stressor frequency and severity on HPA axis activity and cardiometabolic disease may be moderated by psychosocial resilience resources. Resilience resources have previously been defined as characteristics that facilitate a) an individual's recovery from the negative effects of daily stress and b) the maintenance of positive adaptation and wellbeing over time (Diehl, Hay, & Chui, 2012). According to the Daily Stress Process Model (Almeida, 2005), resilience resources interact with various aspects of the stress process to influence the behavioral and biological adaptations to daily stress, resulting in enhanced health and vitality. Resilience resources especially relevant to chronic disease have previously been categorized into five types: 1) personality/dispositional resources, 2) self/ego-related resources, 3) interpersonal/social resources, 4) world views/culturally-based beliefs and values, and 5) behavioral/cognitive skills (Schetter & Dolbier, 2011). Possessing a combination of these types of resilience resources may be particularly beneficial in buffering the negative effects of daily stressors on HPA axis activity and cardiometabolic disease risk.

Optimism, the expectation that good things will happen in the future (Carver, Scheier, & Segerstrom, 2010), is a personality/dispositional resource linked with favorable cortisol profiles and cardiovascular health. In a study of older adults, optimistic individuals experiencing high levels of stress were protected from elevations in daily cortisol and evening cortisol, whereas pessimistic individuals were not (Jobin, Wrosch, & Scheier, 2014). Optimism is also associated with a lower risk of coronary heart disease (Tindle et al., 2009) and cardiovascular mortality (Giltay, Geleijnse, Zitman, Hoekstra, & Schouten, 2004).

Self-esteem is a self/ego-related resource defined as an attitude about the self relevant to assessment of skills, abilities, social relationships, and future outcomes (Heatherton & Wyl, 2003). According to the sociometer hypothesis, the self-esteem system serves as a barometer that responds to threats to social status: When social threat cues are detected, the system triggers unpleasant emotions and, consequently, behaviors necessary to maintain or restore the potential loss of status (Leary, Terdal, Tambor, & Downs, 1995). Self-esteem has a long-demonstrated role in buffering the effects of stress on health, specifically a less severe cortisol (Creswell et al., 2005; Seeman et al., 1995) and cardiovascular response to acute stress (O'Donnell, Brydon, Wright, & Steptoe, 2008). In addition, self-esteem was associated with a steeper cortisol decline throughout the day among a large cohort of U.S. adults (Zilioli et al., 2016).

Social integration is an interpersonal/social resource that describes the subjective quality of one's relationship to society and community (Keyes, 1998). Structural social resources have been associated with lower allostatic load, an index of multisystem physiological dysregulation (Wiley, Bei, Bower, & Stanton, 2017), and low social integration was found to be the strongest predictor of mortality compared to other measures of social relationships (Holt-Lunstad, Smith, & Layton, 2010). Similarly, social isolation was associated with greater cortisol output across the day among men and women (Grant, Hamer, & Steptoe, 2009).

Purpose in life, part of the world views/culturally-based beliefs and values category, describes individuals with "a clear comprehension of life's purpose, a sense of directedness, and intentionality" (Ryff, 1989). Greater purpose in life predicted reduced risk for myocardial infarction over two years (Kim, Sun, Park, Kubzansky, & Peterson, 2013) and predicted lower all-cause mortality among older adults followed for five years (Boyle, Barnes, Buchman, & Bennett, 2009). In a laboratory study, individuals reporting greater purpose in life had more efficient termination of cortisol output following a stressful task (Fogelman & Canli, 2015), highlighting a beneficial role in promoting adaptive cortisol activity.

Positive reappraisal is a behavioral/cognitive skill defined as an adaptive coping process by which stressors are reinterpreted as nonthreatening or useful (Wrosch, Heckhausen, & Lachman, 2000). In women being treated for early stage breast cancer, positive reappraisal was associated with reduced serum cortisol (Cruess et al., 2000). An early study of men recently experiencing their first heart attack found that those who perceived benefits from the heart attack (e.g., changes in life philosophy/values) were less likely to have a subsequent heart attack or experience morbidity 8 years later (Affleck, Tennen, & Croog, 1987).

These resilience resources each demonstrate beneficial associations with cortisol and cardiometabolic disease individually, but may exert synergistic effects when coexisting in high levels (Hobfoll, 2002). For example, higher scores on a composite latent variable of psychosocial resources including self-esteem and optimism were associated with less cortisol reactivity during an experimental stress task, which was significantly greater than the effect of any single psychosocial resource (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007). Thus, possessing high combined levels of resilience resources may mitigate the influence of stressor frequency and severity on cardiometabolic disease via perturbed HPA axis activity.

The purpose of this study was to examine the association of daily stressor frequency and severity with HPA axis activity, resilience resources, and the development of cardiometabolic conditions in a large national sample of U.S. adults. Specifically, the aims of this study were:

1) Determine whether reported daily stressor frequency and daily stressor severity predict greater prevalence of cardiometabolic conditions later in life. Hypothesis 1) Increased exposure to daily stressors (i.e., increased frequency) and increased severity of

daily stressors will both predict greater prevalence of cardiometabolic conditions later in life.

2) Determine whether flattened diurnal cortisol slopes are a mechanism by which increased daily stressor frequency and severity contribute to greater prevalence of cardiometabolic conditions later in life. Hypothesis 2) Flattened diurnal cortisol slopes will partially mediate the effects of stressor frequency and severity on cardiometabolic conditions later in life, such that greater stressor frequency and severity will predict greater cardiometabolic disease prevalence later in life directly, and indirectly via flattened cortisol slopes.

3) Determine whether possessing high levels of resilience resources moderates direct and indirect effects of daily stressor frequency and severity on cardiometabolic disease prevalence later in life. Hypothesis 3) A latent resilience resources variable will moderate the effects of daily stressor frequency and severity on cardiometabolic disease prevalence later in life, such that direct and indirect effects of daily stressor frequency and severity on prevalence of cardiometabolic conditions will be attenuated for individuals reporting greater resilience resources.

METHODS

Participants and Procedures

The present study used data from the *Midlife in the United States* (MIDUS) cohort, a national longitudinal study of health and well-being in the United States. Participants were recruited using random digit dialing and were English-speaking, non-institutionalized adults aged 25 to 74 living in the United States. The initial wave of data (MIDUS 1; N = 7,108) was collected in 1995-1996 to investigate the role of behavioral and psychosocial factors on health and well-being. The original cohort was followed longitudinally, and the second wave of data (MIDUS 2; N = 4,963) was collected in 2004-2005. Seven to nine years later, participants were re-contacted for a third MIDUS survey (MIDUS 3; N = 3,294). Surveys consisted of a phone interview and self-administered questionnaires assessing psychosocial, physical, and mental health. A randomly chosen subset of MIDUS 2 participants also completed the National Study of Daily Experiences 2 (NSDE 2) (N = 2,022), which included daily phone interviews over eight consecutive days and four consecutive days of saliva collection for cortisol analysis during days 2-5 of the phone interviews (see Almeida et al., 2009 for more information). Each night, participants were interviewed via telephone about stressful events they encountered, and reported their activities, behaviors, and emotions in the last 24 hours. Respondents were also asked to provide four daily saliva samples (immediately following waking, 30 minutes post-waking, before lunch, and before bed) in order to assess the diurnal rhythm of cortisol as an indicator of HPA axis function on each day. Eligible participants in the present study were a subset of individuals who took part in the MIDUS 2 survey, NSDE 2, and the MIDUS 3 survey, and who provided saliva samples during NSDE 2 (N = 1,350). The MIDUS study was approved by the Institutional Review Boards of the University of Wisconsin and Pennsylvania State University (coordinating sites).

Measures

Covariates

Demographic variables were assessed at MIDUS 2 and included *age*, *sex* (male = 0, female = 1), *race/ethnicity* (White = 0, non-White = 1), and *education* (less than high school = 1, high school diploma = 2, some college = 3, 4-year college degree or higher = 4).

Medication potentially influencing cortisol activity was measured during the NSDE 2, and included steroid inhalers, steroid medications, cortisone-containing medications, birth control pills, other hormonal medications, and anti-depressant/anti-anxiety medications. *Cortisol-related medication use* was coded as: use of any medication = 1, no use of medications = 0. Participant wake time for each day of saliva sampling was also recorded and entered into the growth curve model predicting salivary cortisol (below).

Health behaviors included smoking status, alcohol intake, and leisure-time moderate-to-vigorous physical activity (MVPA). *Smoking status* was coded as: never smoked = 0, former smoker = 1, current smoker = 2. *Alcohol intake* was operationalized as frequency of consuming at least one alcoholic beverage per day over the past month, and was assessed on a scale from: never = 1 to every day = 6. *Leisure-time MVPA* was assessed by asking participants to rate the frequency of moderate (e.g., "bowling or using a vacuum cleaner") and vigorous (e.g., "running or lifting heavy objects long enough to work up a sweat") physical activity they engaged in during the summer and winter (assessed on a scale from: never = 1 to several times a week or more = 6). Responses in each intensity category were averaged across seasons then summed across intensities. The internal consistency of these four items was high ($\alpha = .91$).

Neuroticism was assessed with 4 items from the Big Five Personality Inventory (Goldberg, 1992). Participants were asked to indicate the extent to which the following words described them, on a scale from 1 = not at all to 4 = a lot: "moody," "worrying," nervous," and "calm" (reverse coded). Neuroticism was calculated as the mean of the 4 items, such that higher scores indicated greater neuroticism. The internal consistency of the measure was adequate (α = .78).

Daily Stressors

Data on daily experiences were obtained during telephone interviews as part of the NSDE 2. The Daily Inventory of Stressful Events (Almeida et al., 2002) was used to assess whether each of 7 types of stressors occurred in the past 24 hours: argument, avoided an argument, stressor at work or school, stressor at home, discrimination, network stressor (i.e., stressful event that happened to a close friend or family member), and any other stressor. *Daily stressor frequency* was calculated by summing the total number of stressors reported over the course of the diary period, then dividing that number by the number of days for which participants provided data. For example, a participant reporting 12 total stressors over the 8-day diary period received a daily stressor frequency score of 1.5. In addition to stressor frequency, participants also reported the severity of each stressor, coded on a scale from: not at all stressful = 0 to very stressful = 3. These scores were summed for each day then averaged across the number of days to create an index of *daily stressor severity*.

Negative Affect

Negative affect was assessed using scales developed for MIDUS 2 (Kessler et al., 2002; Mroczek & Kolarz, 1998). Participants reported the frequency of negative emotions using a 5-point scale from: none of the time = 0 to all of the time = 4. The negative affect scale consisted of 14 items: restless or fidgety, nervous, worthless, so sad nothing could cheer you up, everything was an effort, hopeless, lonely, afraid, jittery, irritable, ashamed, upset, angry, and frustrated. Negative affect was calculated by averaging the items and then averaging scores across interview days. The internal consistency of the negative affect scale was acceptable (α = .80).

Salivary Cortisol

Saliva samples for cortisol analysis were collected using Salivettes (Sarstedt, Rommelsdorft, Germany), in which participants provided samples four times/day on days 2–5 of the 8-day NSDE 2 assessment window. The daily collection time points occurred immediately upon waking, 30 minutes after waking, before lunch, and at bedtime. Cortisol concentrations were analyzed with a commercially available luminescence immunoassay (IBL, Hamburg, Germany). Intra-assay and inter-assay coefficients of variability were both below 5%. Collection compliance was monitored with nightly phone interviews and paper-and-pencil logs included in the collection kits. Samples were excluded if they were missing or exhibited the following assay issues: unreliable assay, missing assay value, empty assay value, assay value > 60 nmol/L, or assay missing a time stamp. Given the strong diurnal nature of cortisol secretion and sensitivity to various circadian influences (e.g., shift work, abnormal sleep patterns, non-compliance to sampling procedures), further exclusion criteria were applied to ensure high-integrity cortisol data (Dmitrieva, Almeida, Dmitrieva, Loken, & Pieper, 2013). Pre-lunch and pre-bedtime samples more than 10 nmol/L above the 30-minute post-awakening value were coded as missing, as a significant surge in cortisol after the awakening response may indicate non-compliance (e.g., eating before sampling). Days were excluded when participants woke before 4 a.m. or after 11 a.m., or were awake more than 20 hours in a day. Finally, the 30-minute post-awakening sample was not included since it is not part of the diurnal slope estimation. After applying these exclusion criteria, the final analytic sample for cortisol consisted of 14,588 saliva samples taken across 5,101 days, provided by 1,333 participants.

Based on established guidelines (Adam & Kumari, 2009), the diurnal cortisol slope was calculated using a 3-level growth curve model using HLM version 7 (Raudenbush & Byrk, 2011), which accounts for the nesting of saliva samples (level 1) within days (level 2) within persons (level 3). Hours since waking and hours since waking^2 were included at level 1 to estimate each participants' diurnal cortisol profile across the three sampling occasions each day. Hours since waking^2 was included because the change in cortisol level across the day is typically nonlinear. Individual mean-centered daily wake up time was included at Level 2, and individual mean wake up time was included at Level 3. Cortisol values were positively skewed, so a log transformation was performed to normalize the data prior to growth curve modeling, as is common in cortisol analysis (Adam & Kumari, 2009). Individual difference cortisol values for time since waking (representing the diurnal slope) were extracted using empirical Bayes residuals (Zilioli, Imami, & Slatcher, 2017), which were standardized for use in the primary analyses.

Resilience Resources

Optimism was assessed using the Revised Life Orientation Test (Scheier, Carver, & Bridges, 1994), which included six items answered on a 5-point Likert scale (0 = a lot disagree to 4 = a lot agree). Sample items were "In uncertain times, I usually expect the best," and "I hardly ever expect things to go my way." Items reflecting pessimism were reverse coded such that higher scores reflected greater optimism. Optimism was operationalized as the sum of the six items. The internal consistency of the scale was good (α = .80).

Self-esteem was measured using a modified version of the Rosenberg Self-Esteem Scale (Rosenberg, 1965), which comprised seven items answered on a 7-point Likert scale (1 = strongly agree, 7 = strongly disagree). Sample items included: "On the whole, I am satisfied with myself" and "I take a positive attitude toward myself." For participants who answered at least four items on the scale, ratings were summed to create a self-esteem score. Higher scores indicated higher self-esteem. The scale had adequate internal consistency (α = .76).

Social integration was assessed as part of the MIDUS survey's social wellbeing questionnaire (Keyes, 1998). Three items were scored on a 7-point Likert-type scale (1 = strongly agree, 7 = strongly disagree). The items were: "I don't feel I belong to anything I'd call a community," "I feel close to other people in my community," and, "My community is a source of comfort." The negative item was reverse coded so that higher scores reflected greater social integration. Social integration was operationalized as the sum of the three items. The scale had adequate internal consistency (α = .73).

Purpose in life was measured with the Ryff Scales for Psychological Wellbeing (Ryff, 1989). Seven items were scored on a 7-point Likert-type scale (1 = strongly disagree, 7 = strongly agree). Sample items included: "I have a sense of direction and purpose in life," "I enjoy making plans for the future and working to make them a reality," and "I sometimes feel as if I've done all there is to do in life" (reverse coded). Purpose in life was operationalized as the sum of the seven items. The scale had adequate internal consistency (α = .70).

Positive reappraisal was assessed using four items as part of a scale measuring coping strategies (Wrosch et al., 2000). Sample items included "I find I usually learn something meaningful from a difficult situation," and "I can find something positive, even in the worst situations." Participants responded on a scale from 0 (not at all) to 3 (a lot). Positive reappraisal was operationalized as the mean of the four items. The internal consistency of the scale was adequate ($\alpha = .78$).

Cardiometabolic Conditions

At MIDUS 2 and MIDUS 3, participants were provided with a list of chronic health conditions and asked to indicate those they had experienced or been treated for during the previous year. Participants were also asked whether they had taken prescription medication for heart disease, hypertension, type 2 diabetes, or cholesterol in the past 30 days. Reporting "yes" to either being treated or taking medication for a given condition was coded as 1. Participants were also asked to self-report their height and waist circumference, from which Waist to Height Ratio (WHtR) was calculated (waist in inches/height in inches). Based on established guidelines, obesity was defined as WHtR $\geq$ 0.60 (Ashwell & Gibson, 2016) and also coded as: obese = 1, not obese = 0. Values for each condition were summed to create a summary cardiometabolic conditions score, ranging from 0 to 6, with higher scores indicating greater prevalence of cardiometabolic conditions. Given the high prevalence of cardiometabolic conditions in this study's sample, the distributions of scores at MIDUS 2 and 3 were approximately normal and did not demonstrate the zero-inflated profile of typical count data. Thus, these variables were treated as continuous in analyses.

Statistical Analyses

Data Preparation and Preliminary Analyses

Of the 1,350 eligible participants, 1,333 were included in the analyses after applying exclusion criteria for salivary cortisol (see Figure 8 for determination of final analytic sample). All analyses except for growth curve modeling of salivary cortisol were performed using *Mplus* version 7.4 (Muthen & Muthen, 2015). Full-information maximum likelihood (FIML) estimation was used to handle missing data. FIML is a robust missing data approach that uses all available data to estimate each model path while also providing unbiased standard errors, based on actual available data for a given parameter estimate (Enders, 2010). Missing data prevalence for variables of interest was: daily stressor severity: 8%; resilience resources indicators: 2-3% for all; MIDUS 2 cardiometabolic conditions: 18%; MIDUS 3 cardiometabolic conditions: 23%. Missing on MIDUS 2 covariates ranged from 0-6%.

To test hypotheses 1-3, structural equation modeling (SEM) was performed. First, a resilience resources latent variable was constructed using each of the five measured resilience resources. Confirmatory factor analysis assessed factor loadings and variance explained by the latent variable, and a measurement model was created using the above five variables correlated together, and tested for goodness of fit according to traditional criteria (Browne & Cudeck, 1992): χ^2, Standardized Root Mean Square Residual (SRMR; acceptable fit threshold: < 0.05), Root Mean Square Error of Approximation (RMSEA; acceptable fit threshold: $\leq$ 0.08), Comparative Fit Index (CFI), and Tucker Lewis Index (TLI; acceptable fit threshold for CFI and TLI: 0.95-1.00).

Main Analyses

Primary analyses were performed in 3 steps according to the latent moderated structural equation method (Maslowsky, Jager, & Hemken, 2015). The step 1 structural model (Model 1/null model) estimated direct effects of daily stressor frequency, daily stressor severity, and resilience resources (latent) on diurnal cortisol slopes and MIDUS 3 cardiometabolic conditions, and indirect effects on MIDUS 3 cardiometabolic conditions via the diurnal cortisol slope. Traditional model fit statistics and path coefficients were obtained. In steps 2 and 3, latent variable interaction terms were created from resilience resources and daily stressor frequency, and from resilience resources and daily stressor severity, respectively, and added to otherwise-identical models predicting diurnal cortisol slope and MIDUS 3 cardiometabolic conditions. Model 2A (containing the daily stressor frequency interaction term) and 2B (containing the daily stressor severity interaction term) were compared to the null model (model 1) using the log-likelihood ratio test to determine whether model 1 represented a loss of fit relative to Models 2A and 2B. MIDUS 2 covariates (age, sex, race/ethnicity, education, smoking status, alcohol intake, leisure-time MVPA, neuroticism, and MIDUS 2 cardiometabolic conditions) were adjusted for on all paths in Models 1, 2A and 2B. Cortisol-relevant medication use was also included on all paths estimating diurnal cortisol slopes. All continuous variables were standardized prior to inclusion in the models. A conceptual model illustrating Models 2A and 2B is shown in Figure 9.

RESULTS

Descriptive information of the study sample is provided in Table 7. Five observed resilience resources indicators (optimism, self-esteem, social integration, purpose in life, and positive reappraisal) were used to estimate a measurement model prior to structural equation modeling. The initially-specified model fit the data well (χ^2 = 8.347, *df* = 4, *p* = 0.0796; RMSEA = 0.029, SRMR = 0.011, CFI = 0.998, TLI = 0.995). Factor loadings were all above 0.45 and are shown in Figure 10.

Model 1 Results

The fit of Model 1 was acceptable based on three criteria (CFI = 0.963, RMSEA = 0.042; SRMR = 0.021), but was suboptimal according to one threshold (TLI = 0.930).

The fairly large chi-square statistic was significantly different from zero (χ^2 = 194.595, *df* = 171, $p < 0.001$), although the χ^2 statistic is sensitive to large sample sizes.

Model 1 path estimates predicting diurnal cortisol slope and MIDUS 3 cardiometabolic conditions are shown on the left-hand columns of Table 8. A graphic depiction of Model 1, including factor loadings, is show in in Figure 10. Non-White race/ethnicity, MIDUS 2 cardiometabolic conditions, smoking status, and cortisol-related medication use were all associated with flattened diurnal cortisol slopes. However, neither stressor frequency, stressor severity, nor resilience resources were not associated with diurnal cortisol slopes. Flattened cortisol slopes (95% CI [0.013, 0.106]) and increased daily stressor severity (95% CI [0.022, 0.125]) both predicted greater prevalence of MIDUS 3 cardiometabolic conditions, as did age and MIDUS 2 cardiometabolic conditions. Female sex, alcohol intake, and leisure-time MVPA were associated with fewer MIDUS 3 cardiometabolic conditions. Resilience resources were not associated with MIDUS 3 cardiometabolic conditions, although the bulk of the confidence interval fell in the region indicating an association with lower prevalence (95% CI [-0.124, 0.001]). Hypothesis 1 was partially supported: greater stressor severity, but not stressor frequency, was associated with greater cardiometabolic disease prevalence at MIDUS 3.

Given the significant association of stressor severity and MIDUS 3 conditions, the indirect effect of daily stressor severity on MIDUS 3 cardiometabolic conditions via cortisol slopes was examined. The indirect effect was not different from zero (β = -0.001, 95% CI [-0.005, 0.002]), thus not supporting hypothesis 2.

Model 2 Results

The moderation of resilience resources on associations of daily stressor frequency with diurnal cortisol slopes and MIDUS 3 cardiometabolic conditions was tested in model 2A. The log-likelihood ratio test was performed to determine whether model 1 represented a loss of fit relative to model 2. The test statistic was not significant (D = 3.622, df = 2, p > 0.05), indicating that model 1 represented a loss of fit relative to the more complex model 2. The stressor frequency x resilience resources interaction term was not associated with diurnal cortisol slopes (95% CI [-0.044, 0.058]) or MIDUS 3 cardiometabolic conditions (95% CI [-0.052, 0.035]), thus not supporting moderation and hypothesis 3 (middle columns of Table 8).

The moderation of resilience resources on associations of daily stressor severity with diurnal cortisol slopes and MIDUS 3 cardiometabolic conditions was tested in model 2B. The sample size for model 2B was reduced to N = 1,222 due to 111 missing cases on daily stressor severity, which precluded construction of the latent interaction term for those cases. The log-likelihood ratio test was performed to determine whether model 1 represented a loss of fit relative to model 2B. The D test statistic was significant (p < 0.001), indicating that model 1 represented a loss of fit relative to the more complex model 2. The stressor frequency x resilience resources interaction term was not associated with diurnal cortisol slopes (95% CI [-0.028, 0.086]) or MIDUS 3 cardiometabolic conditions (95% CI [-0.034, 0.063]), thus not supporting moderation and hypothesis 3 (right-hand columns of Table 8).

DISCUSSION

The present study examined associations between daily stressor frequency and severity, diurnal cortisol slopes, resilience resources, and future prevalence of cardiometabolic health conditions. Findings indicated that greater daily stressor severity and flattened diurnal cortisol slopes predicted greater prevalence of cardiometabolic conditions later in life, controlling for baseline cardiometabolic conditions. Diurnal cortisol slopes did not mediate the association of daily stressor severity with cardiometabolic conditions, and resilience resources did not moderate associations of daily stressor frequency and severity with diurnal cortisol slopes and cardiometabolic conditions. These results extend literature by demonstrating prospective associations of increased daily stressor severity and flattened diurnal cortisol slopes with cardiovascular and metabolic health outcomes.

The most noteworthy finding of the present study was the association of greater perceived stressor severity with greater prevalence of cardiometabolic conditions many years later, independent of stressor frequency, neuroticism, and negative affect. Perceived stressor severity is often considered to be a function of trait characteristics, most commonly neuroticism (Lahey, 2009). Although perceptions of stressor severity are subjective, that perceived stressor severity demonstrated an association with greater prevalence of cardiometabolic conditions at MIDUS 3 independent of neuroticism suggests that modifiable aspects of stressor appraisal may be more relevant to physical health. Levels of negative affect often explain associations of stressors with physical health outcomes (Longua, DeHart, Tennen, & Armeli, 2009; Ormel, Riese, & Rosmalen, 2012), so the fact that stressor severity was associated with cardiometabolic conditions independent of negative affect indicates that perceived stressfulness of daily events may be a unique determinant of physical health.

The prospective association of perceived stressor severity with cardiometabolic conditions extends the current stressor severity literature, which shows cross-sectional associations with mental health outcomes, wellbeing, and physical symptoms. One such study demonstrated that stressor severity partially mediated the association between lower SES and greater number of physical health symptoms (Almeida, Neupert, Banks, & Serido, 2005), while another cross-sectional study found that greater lifetime stress severity was associated with greater mental and physical health symptoms (Toussaint, Shields, Dorn, & Slavich, 2016). The current study's results substantially expand the current state of stressor severity and health research by moving beyond mental health and physical symptoms, which are more direct correlates of stressor appraisal. The present study's finding of perceived stressor severity being associated with cardiovascular and metabolic health outcomes many years later shows that increased perceived stressor severity has more broad, downstream influences on health.

The present study's finding of flattened diurnal cortisol slopes predicting greater prevalence of cardiometabolic conditions at MIDUS 3 reflects previous cross-sectional research, and adds much-needed prospective data characterizing the association between cortisol slopes and cardiometabolic health. In a recent meta-analysis examining associations of diurnal cortisol slopes and health outcomes, flattened slopes were associated with higher rates of obesity, type 2 diabetes, and cardiovascular disease (Adam et al., 2017); however, nearly all of those studies were cross-sectional. One of the few longitudinal studies found that flattened cortisol slopes were associated with increased risk of mortality due to cardiovascular disease 6-8 years later (Kumari et al., 2011). The current study finding, independent of traditional behavioral risk factors including alcohol intake, smoking status, and physical activity, demonstrates that flattened diurnal cortisol slopes play a role in cardiovascular and metabolic health over time.

Alternative to the proposed hypotheses, resilience resources did not moderate associations of daily stressor frequency or severity with diurnal cortisol slopes or MIDUS 3 cardiometabolic conditions, which may be due to the time-frame in which stressors were assessed. The resilience resources used to create the latent variable have previously demonstrated beneficial influences in the context of *chronic* stress (Schetter & Dolbier, 2011). In the present study, measures of stressor frequency and severity were taken daily during an 8-day interview, representing more *acute* challenges. It is not known to what degree the 8-day snapshot reflects the broader and cumulative stress burden of participants' lives. An additional potential explanation for null findings is that although model fit indices suggested that the resilience resources latent variables was well-constructed, factor loadings were somewhat low for social integration (.517) and positive reappraisal (.466). These two constructs, although representing domains of resilience relevant to physical health (Schetter & Dolbier, 2011), are perhaps conceptually more distinct from the other three resources optimism, self-esteem, and purpose in life. Future research should examine resilience resources in the context of day-to-day stress, with particular emphasis on comparing resources from different resilience domains (e.g., dispositional resources vs. social resources vs. cognitive skills).

The results of the present study should be considered in light of several limitations. First, the sample was over 90% White, which limits generalizability of findings to groups from diverse racial/ethnic backgrounds. Particularly noteworthy was the finding that diurnal cortisol slopes were much flatter among racial/ethnic minority participants compared White participants. Given the small sample size of non-White participants (less than 7% of the full sample), exploring this finding further by conducting a subgroup analysis or a multigroup comparison, for example, would be statistically challenging. A second limitation is the staggered timing of MIDUS 2 and NSDE 2 measures. The focal predictors (daily stressor frequency and severity) and the proposed mediator (salivary cortisol) were assessed up to 1-2 years after the MIDUS 2 measures were collected. Thus, the MIDUS 2 covariates were collected many months to years prior to the NSDE 2. This time discrepancy may have accounted for a lack of expected association and interaction with resilience resources in the structural models. A final limitation involves the 12-month time period in which participants were asked whether or not they had been treated or experienced a cardiometabolic health condition. It is likely that some participants had experienced—but then recovered from—conditions one or many years prior, which would not have registered during the ascertained 12-month time period. Thus, the summed MIDUS 3 cardiometabolic condition outcome likely underestimated the true occurrence of those conditions during the follow-up period.

In addition to these limitations, the study also had numerous strengths which should engender confidence in the findings. The use of daily diary methods to assess stressor frequency, severity, and negative affect over eight consecutive days provided a detailed glimpse of day-to-day living with high ecological validity that limited the recall bias common of traditional questionnaires. Another study strength was the rigorous analysis of salivary cortisol, including both the exclusion of samples and days on which participants exhibited circadian rhythm-disrupting behavior and the use of 3 level growth curve modeling to estimate individual differences in diurnal cortisol slopes. Many studies assessing salivary cortisol in psychological and health research employ few exclusion criteria in order to maximize sample size, but the sensitivity of cortisol to circadian disruption suggests that more stringent inclusion standards may be warranted.

In summary, this study found that increased perceived severity of daily stressors and flattened diurnal cortisol slopes were both associated with greater prevalence of cardiovascular and metabolic health conditions later in life. These findings extend literature characterizing stressor severity and cortisol slopes in the context of physical health, which have thus far been limited almost exclusively to cross-sectional findings. Future research should examine whether resilience resources more closely linked with daily stressors moderate associations of stressor severity and flattened cortisol slopes with cardiometabolic conditions.

Table 7. Descriptive Information of the study sample (N = 1,333 to N = 1,096).

Variables	Mean (SD)
Demographic, lifestyle, and psychological covariates	
Age, years	55.58 (11.31)
Sex, n female (%)	746 (56)
Race/ethnicity, n non-White (%)	85 (6.4)
Educational attainment, n > college degree (%)	578 (43)
Smoking status, n never smoked (%)	769 (58)
Alcohol intake	1.99 (1.81)
Leisure-time MVPA	7.63 (3.29)
Neuroticism	2.01 (0.62)
Daily Diary Variables	
Daily stressor frequency	0.54 (0.44)
Daily stressor severity	1.73 (0.62)
Negative affect	0.17 (0.20)
Salivary Cortisol and Related Measures	
Wake up time, hour	6.71 (1.07)
Cortisol-related medication use, n yes (%)	526 (46)
Waking cortisol, nmol/L, median (IQR)	14.73 (8.40)
Pre-lunch cortisol, nmol/L, median (IQR)	6.25 (4.10)
Pre-bed cortisol, nmol/L, median (IQR)	2.09 (2.43)
Diurnal cortisol slope, standardized	0.00 (1.00)
Resilience Resources	
Optimism	23.99 (4.58)
Self-Esteem	38.61 (7.04)
Social Integration	15.13 (3.98)
Purpose in Life	39.54 (6.56)
Positive Reappraisal	3.08 (0.60)
Cardiometabolic Conditions	
MIDUS 2 cardiometabolic conditions, sum	1.06 (1.20)
MIDUS 3 cardiometabolic conditions, sum	1.56 (1.42)

Note. All data provided as mean (SD) unless indicated otherwise. Cortisol provided in raw values. MVPA = moderate-to-vigorous physical activity; IQR = interquartile range.

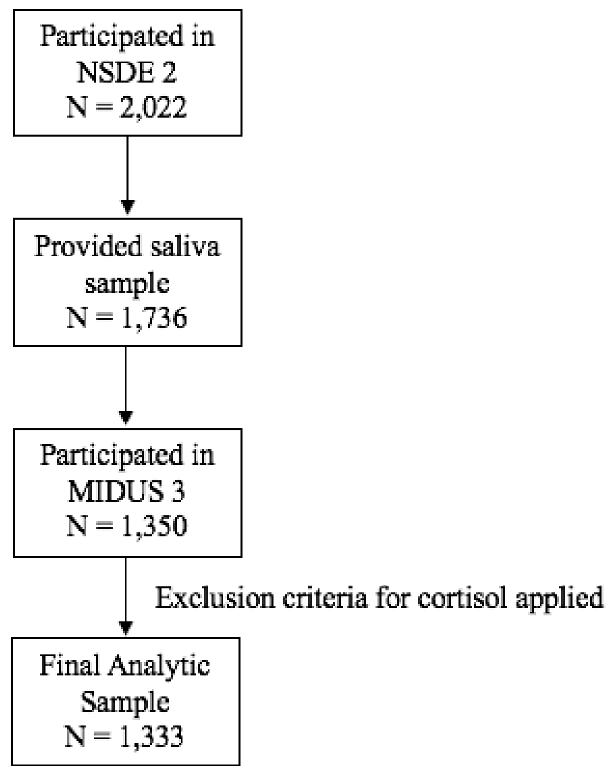

Figure 8. Flowchart depicting reduction from initial sample to final analytic sample size. NSDE = National Study of Daily Experiences.

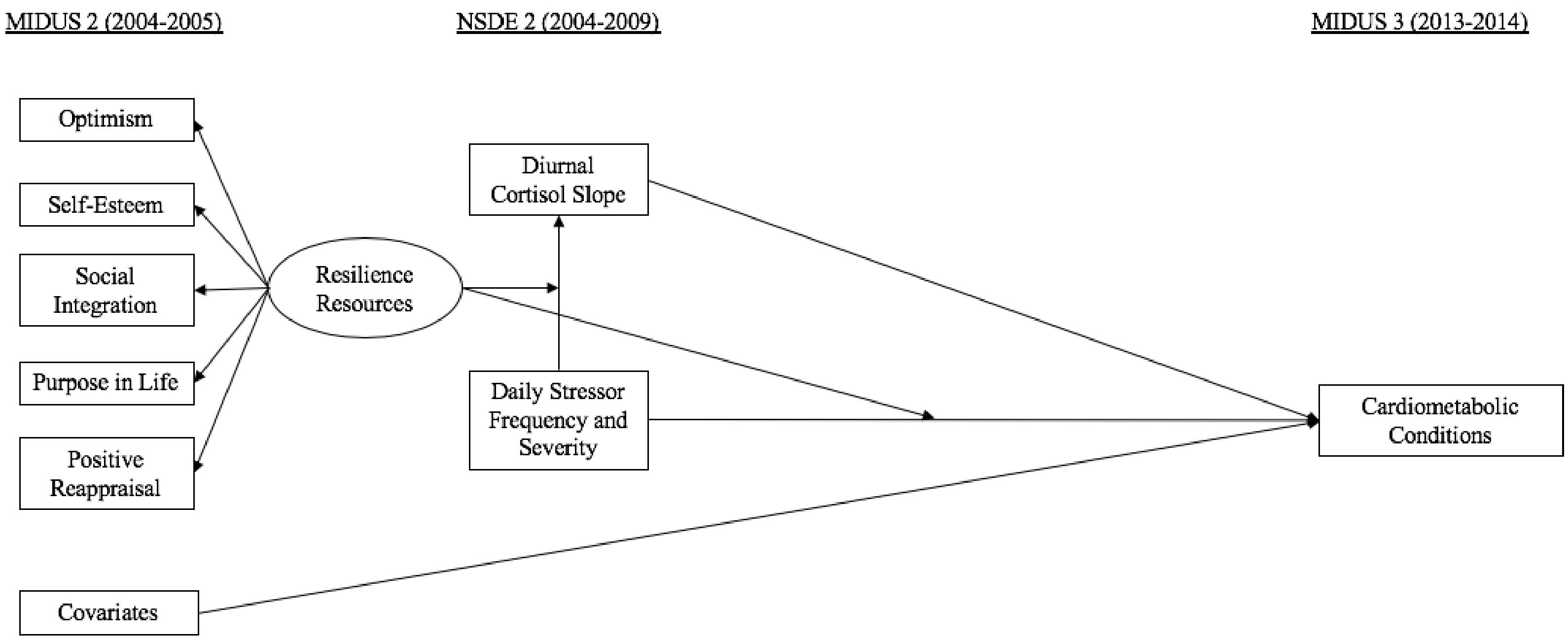

Figure 9. Conceptual model depicting hypothesized associations among variables and times at which variables were measured. NSDE = National Study of Daily Experiences. Model 2A examines daily stressor frequency as the focal predictor, while Model 2B examines daily stressor severity as the focal predictor.

Table 8. Standardized coefficients from structural equation models predicting diurnal cortisol slope and MIDUS 3 cardiometabolic conditions (N = 1,333 for Models 1 and 2A; N = 1,222 for Model 2B).

	Diurnal Cortisol Slope			MIDUS 3 Cardiometabolic Conditions		
	Model 1	Model 2A	Model 2B	Model 1	Model 2A	Model 2B
Variables	β	β	β	β	β	β
Age	0.050	0.050	0.048	0.141***	0.141***	0.139***
Sex	0.114	0.115	0.130*	-0.193***	-.193***	-0.173***
Non-White race/ethnicity	0.386***	0.386***	0.351**	0.016	0.017	0.024
Education	-0.037	-0.037	-0.043	-0.034	-0.034	-0.027
M2 cardiometabolic conditions	0.107**	0.107**	0.110**	0.612***	0.613***	0.605***
Smoking status	0.203***	0.231***	0.246***	-0.011	-0.011	-0.019
Alcohol intake	-0.019	-0.019	-0.023	-0.050*	-0.050*	-0.045
Leisure-time MVPA	-0.001	-0.001	0.024	-0.058*	-0.057*	-0.055*
Neuroticism	-0.055	-0.056	-0.051	-0.007	-0.007	-0.025
Cortisol-related medication use	0.134*	0.134	0.142*	-	-	-
Negative Affect	0.056	0.058	0.057	-0.047	-0.049	-0.044
Daily Stressor Frequency	-0.035	-0.034	-0.034	-0.005	-0.005	-0.001
Daily Stressor Severity	-0.023	-0.024	-0.026	0.074**	0.074**	0.074**
Resilience Resources	-0.038	-0.039	-0.045	-0.062	-0.062	-0.081*
Stressor Freq x Resil Res	-	0.007	-	-	-0.009	-
Stressor Severity x Resil Res	-	-	0.029	-	-	0.015
Diurnal Cortisol Slope	-	-	-	0.060*	0.060*	0.059*
Model R^2	0.080	0.081	0.86	0.525	0.525	0.510
F for R^2	5.532***	5.526***	5.418***	23.713***	23.721***	21.763***
F for R^2 change	-	1.631	1.909	-	1.775	1.886

Note. Sex (Male = 0, Female = 1). M2 = MIDUS 2; MVPA = moderate-to-vigorous physical activity. *, $p < .05$; **, $p < .01$; ***, $p < .001$.

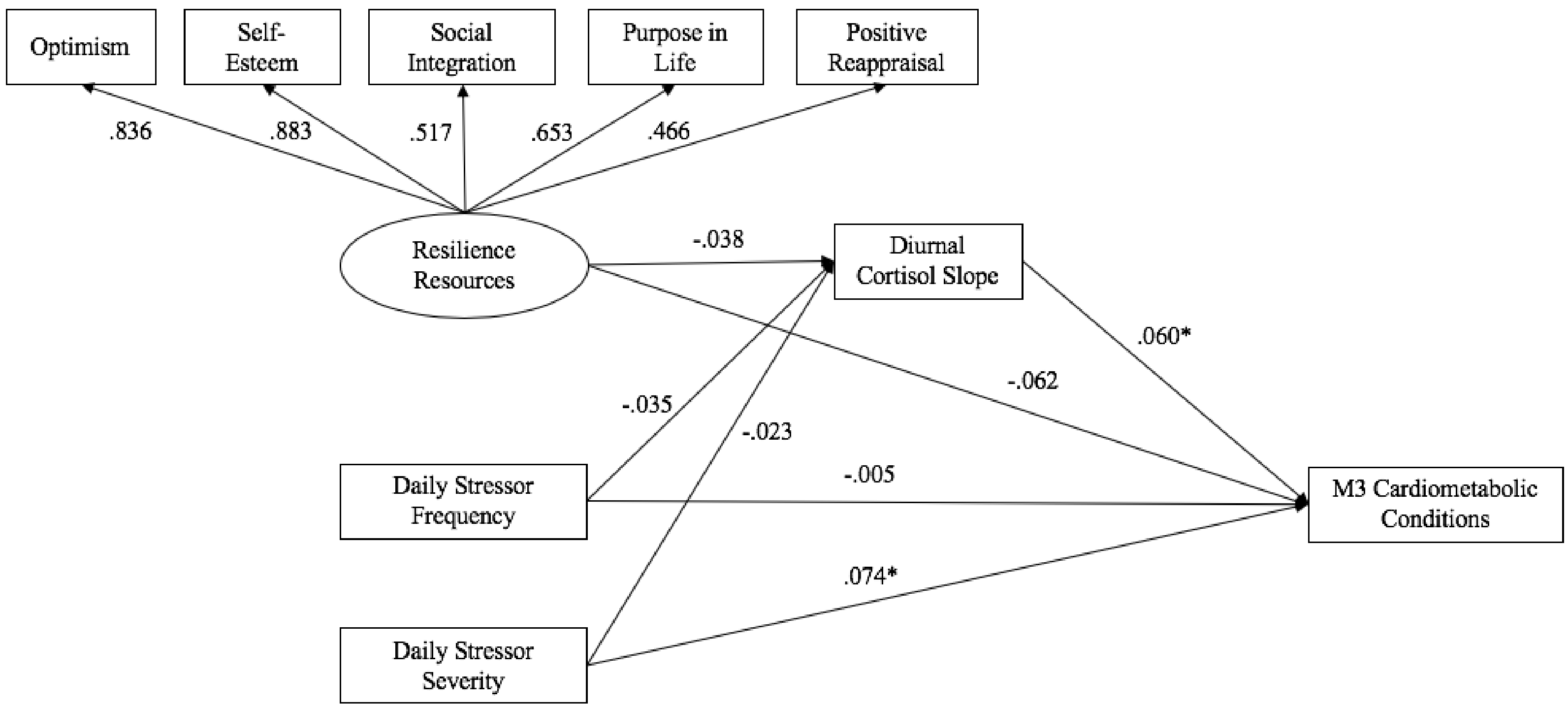

Figure 10. Standardized path coefficients from structural equation Model 1 predicting diurnal cortisol slope and MIDUS 3 cardiometabolic conditions. To improve the clarity of the figure, covariates, correlations, and disturbances are not included.

Chapter 5: Discussion

SUMMARY OF FINDINGS

Study 1 examined associations between race, perceived everyday discrimination, and hair cortisol concentration. The principle finding was that perceived discrimination frequency was associated with greater hair cortisol concentration among African American but not White adults. Perceived discrimination did not mediate the association of African American race with elevated hair cortisol concentration, which was due to similar reported perceived discrimination scores among African American and White participants. White participants reported greater age- and physical appearance-based attributions for discrimination, while African Americans' discrimination scores were driven largely by race-based attributions. Taken together, these findings suggest that perceived discrimination is a source of HPA axis-related stress for African Americans, and that aspects of discrimination other than frequency of occurrence (e.g., uniqueness of African American experience with discrimination) may account for observed racial differences.

Study 2 investigated the allostatic load model more completely, examining the association of perceived stress with MetS severity, hair cortisol concentration as a mediator, and resilience as a moderator. In main effects analyses, perceived stress was not associated with MetS severity directly or indirectly via hair cortisol concentration. However, resilience moderated the association of perceived stress and hair cortisol concentration, such that perceived stress was associated with greater hair cortisol concentration among low-resilience individuals. Furthermore, the moderation by resilience was transmitted to MetS severity, such that for low-resilience individuals, perceived stress was associated elevated hair concentration, which was associated with greater MetS severity. Greater resilience was also directly associated with lower MetS severity, suggesting dual benefits of resilience as a both a stress buffer and direct determinant of favorable cardiometabolic health.

Study 3 extended the research questions in Study 2 to a longitudinal framework, examining associations of daily diary-assessed stressor frequency and severity with prevalence of cardiovascular and metabolic conditions in the national MIDUS cohort. Perceived stressor severity, but not stressor frequency, was associated with elevated prevalence of cardiometabolic conditions. Additionally, flattened diurnal cortisol slopes were also associated with greater future prevalence of cardiometabolic conditions. Resilience resources displayed a near-significant inverse association with future cardiometabolic conditions, but resilience resources did not interact with either stressor frequency or severity to predict diurnal cortisol slopes or future cardiometabolic condition prevalence. The results of Study 3 indicate that stressor severity and flattened diurnal cortisol slopes may be determinants of cardiovascular and metabolic disease over time.

SYNTHESIS OF FINDINGS

Common Findings Across Studies

Studies 1-3 produced many common findings across studies, promoting confidence in their replicability. First, Studies 2 and 3 both found associations of altered HPA axis activity—elevated hair cortisol concentration and flattened diurnal cortisol slopes, respectively—with cardiometabolic health outcomes. These corresponding findings are encouraging given substantial differences between Studies 2 and 3 in cortisol medium (i.e., hair vs. saliva), sample composition (i.e., ethnically and socioeconomically diverse vs. primarily White and well-educated), and study design (i.e., cross-sectional vs.

longitudinal). These findings are aligned with prior cross-sectional research showing associations of hair cortisol with a variety of MetS-related outcomes (Jackson et al., 2017; Kuehl et al., 2015; Stalder et al., 2013), and of flattened cortisol slopes with a host of cardiovascular and metabolic outcomes (Adam et al., 2017; Hackett et al., 2016; Kumari et al., 2011). Thus, studies 2 and 3 support the role of altered HPA axis activity in cardiovascular and metabolic health complications.

A second common finding was the existence of racial/ethnic differences in cortisol output. Study 1 found that African Americans had elevated hair cortisol levels, while Study 3 demonstrated that non-White participants had flatter diurnal cortisol slopes compared to White participants. These findings reflect prior research showing that racial minority groups tend to have elevated evening cortisol levels (Cohen et al., 2006; DeSantis et al., 2007). The reasons for these differences are not entirely clear. For hair cortisol, African Americans have slower hair growth rate which may allow cortisol more time to accumulate into hair follicles, reflected in elevated cortisol levels in scalp hair (Wosu et al., 2015). However, given the paucity of studies examining correlates of hair cortisol among racial minority groups, attempts at an explanation are premature. Differences in cortisol slopes are quite common among racial minority groups, and are considered to be due in part to stress-related factors (DeSantis, Adam, Hawkley, Kudielka, & Cacioppo, 2015). Although findings from Studies 1 and 3 support racial/ethnic differences in HPA axis output, more research on why these differences exist is warranted.

Finally, Studies 2 and 3 both found direct associations of greater resilience with more favorable cardiometabolic health, although Study 3 findings should be interpreted cautiously given that the association of resilience resources and cardiometabolic conditions did not meet the threshold for statistical significance ($p = 0.052$). In the case of

Study 2, higher resilience scores were associated with lower MetS severity, while in Study 3, possessing greater resilience resources were associated with lower prevalence of cardiometabolic conditions. Past research shows that greater resilience is associated with lower BMI and waist circumference (Stewart-Knox et al., 2012), lower T2D incidence (Crump et al., 2016), and improved A1C over 1 year follow-up among individuals with T2D (Yi et al., 2008), independent of stress-buffering effects. Studies 2 and 3 align with this literature and suggest that resilience can be beneficial for cardiometabolic health in its own right.

Inconsistent Findings Across Studies

Although similar results across Studies 1-3 promote confidence in the reported findings, there were also disparate outcomes that offer opportunity for scrutiny and provide guidance for future research. Notably, associations of various types of psychosocial stress with cortisol indices and health outcomes were variable and often dependent on moderation. In Study 1, perceived everyday discrimination was not associated with hair cortisol concentration in the full sample, and was only positively associated with hair cortisol levels among African Americans. Similarly, Study 2 found that perceived stress was only associated with hair cortisol concentration (and with MetS indirectly) for individuals reporting low levels of resilience. On the other hand, daily stressor frequency was associated with neither cortisol slopes nor cardiometabolic conditions, regardless of interaction with resilience resources in Study 3. Across all studies, the only stressor type directly associated with cortisol or a health outcome was daily stressor severity, positively associated with future cardiometabolic conditions in Study 3. It is somewhat surprising that this was the only significant main effect given the time elapsed between daily stressor severity assessment and MIDUS 3 cardiometabolic conditions and the well-controlled analyses. However, those methodological strengths of Study 3 indicate that stressor severity is likely a determinant of cardiovascular and metabolic health.

In Study 2, resilience moderated the association of perceived stress and hair cortisol concentration, such that the association between perceived stress and hair cortisol concentration was stronger for participants reporting low resilience. This finding was not observed in Study 3, which found that resilience resources did not moderate associations of stressor frequency or stressor severity with diurnal cortisol slopes and cardiometabolic conditions. Differences between studies could be due to all variables being measured at the same time in Study 2, while months to years elapsed between resilience resource measurement and daily stressor characteristics in Study 3. Additionally, the conceptualization of resilience differed across studies. Resilience was defined as simply "the ability to bounce back or recover from stress" (Smith et al., 2008) in Study 2, but was more loosely described as a clustering of psychosocial resources previously demonstrated to protect against detrimental effects of chronic stress on disease in Study 3 (Schetter & Dolbier, 2011). The inconsistent ability of resilience to moderate associations of stress with cortisol and cardiometabolic health emphasizes the importance of defining resilience, which remains a point of contention among scholars (Aburn, Gott, & Hoare, 2016).

CONTRIBUTIONS TO THE FIELD

Collectively, results from Studies 1-3 make important advances in stress physiology and social determinants of health research. Although it must be replicated, the finding of race moderating the association between perceived discrimination and hair cortisol concentration suggests that increased perceived discrimination is associated with

HPA axis upregulation among African Americans. The literature examining racial group differences in the association of discrimination and cortisol indices has been quite mixed (Busse et al., 2017; Korous, Causadias, & Casper, 2017), with methodological shortcomings in cortisol assessment likely contributing to the equivocal state of the current research. Hair cortisol, as a more stable and retrospective index of HPA axis activity over several months, may have been a better-matched measure of HPA function for the type of discrimination scale used in the present study. If the finding from Study 1 hold up to future investigation, it represents a potential mechanism by which discrimination can "get under the skin" and undermine health for African Americans experiencing heightened discrimination.

Study 2 findings enhance allostatic load and hair cortisol research on multiple fronts. First, in testing hypothesized mediating and moderating constructs of the allostatic load model in the same model, Study 2 provides a comprehensive investigation into the synergistic processes at the heart of the allostatic load model. Studies often test individual paths (e.g., from perceived stress to cortisol, or from cortisol to health outcome) and perhaps mediation or moderation. The finding that perceived stress was associated with MetS severity indirectly via elevated hair cortisol concentration only among low-resilience individuals demonstrates the importance of testing mediation and moderation in the same model. Study 2 results also provide some explanation for the consistent null associations of general perceived stress with hair cortisol concentration (Stalder et al., 2017), implying that individual differences in the ability to adapt to stress should be taken into account when considering associations of perceived stress with hair cortisol levels. The finding of elevated hair cortisol concentration associated with greater MetS severity is also a significant contribution, given that nearly all of the work examining associations of hair cortisol with cardiovascular and metabolic health has been conducted in White samples.

Prospective findings of flattened diurnal cortisol slopes and greater stressor severity with cardiometabolic conditions in Study 3 are both substantial contributions to the understanding of the stress-related etiology of cardiovascular and metabolic disease. A large body of evidence supports cross-sectional associations of flattened cortisol slopes with poor physical health outcomes, but very few have tested longitudinal relationships (Adam et al., 2017). The finding from Study 3 suggests that altered HPA axis activity in the form of flattened cortisol slopes may influence cardiovascular and metabolic health over time. Furthermore, the association of stressor severity with MIDUS 3 cardiometabolic conditions, which was robust to adjustment for stressor frequency, neuroticism, and negative affect, implies that inherent stressfulness and/or aspects of stress appraisal are related to cardiometabolic health independent of related personality and mood factors. Disentangling the relative contributions of objective and subjective stressor severity to cardiometabolic health represents an exciting avenue for future investigation.

BROADER IMPLICATIONS OF THE FINDINGS AND DIRECTIONS FOR FUTURE RESEARCH

Although contributions to the scientific field are important, the ultimate value of this (and most) research lies in its ability to produce tangible benefits beyond academia. The results of Study 1 suggest that perceptions of discrimination are a relevant stressor for HPA axis output among African Americans. While this finding is not causal, it suggests a plausible pathway by which discrimination could influence physical health for this racial group. The simple knowledge that discrimination could contribute to disease may be eye-opening for many persons, and potentially make such individuals reconsider their actions towards African Americans. This knowledge may also inform policy designed to reduce the prevalence of discrimination on a national scale. To address the issue of the stressfulness of discrimination more directly, it may be worthwhile to consider interventions that assist African Americans in handling encounters with discrimination in a manner that would reduce HPA axis activation, such as incorporating cognitive behavioral therapy or positive reframing. It should also be noted, however, that discrimination is likely only one of many challenges in African Americans' lives, and that other challenges including neighborhood safety, family issues, and financial strain may have also influenced the HPA axis for these individuals. Future research should more comprehensively assess various hardships among African Americans to determine which sources of life stress may be contributing to HPA axis upregulation in this population.

The findings of large racial/ethnic differences in diurnal cortisol slopes in Study 3 invites inquiry into psychosocial determinants of those differences, and examining racial group differences between stressor types, cortisol indices, and health outcomes is warranted. The current racial/ethnic homogeneity of the MIDUS cohort is not ideally-suited for these analyses, but perhaps other nationally-representative datasets can provide opportunities for this work in the future. Given that elevated hair cortisol concentration and flattened diurnal cortisol slopes indicate different aspects of HPA axis function and were both associated with cardiometabolic health, future studies should examine hair and salivary cortisol in same study, ideally prospectively. The flattened diurnal slope is considered a hallmark of chronic stress and burnout, whereas elevated HPA axis output in the form of elevated hair cortisol levels may reflect vigilance or a priming effect due to hyper-arousal of living in threatening environments (Miller et al., 2007; Stalder et al., 2017). A life-course perspective is needed to determine whether, and at what point, individuals under chronic stress may shift from generally elevated cortisol levels to flattened cortisol decline throughout the day.

Whether diurnal cortisol slopes represent modifiable targets for intervention remains to be seen. In a daily diary study, increased anger and tension were associated with flattened diurnal cortisol slopes on the same day (Adam, Hawkley, Kudielka, & Cacioppo, 2006), suggesting the diurnal slope reflects emotions of daily living. However, interventions targeting cortisol as an outcome of stress-related behavioral interventions are limited. A novel guided imagery lifestyle pilot intervention in obese Latino adolescents identified salivary and serum cortisol as primary outcomes, and demonstrated acute reductions in salivary cortisol and improved insulin sensitivity associated with reduced serum cortisol (Weigensberg et al., 2014). A larger randomized trial is underway (Weigensberg et al., 2018), which could provide crucial data on whether cortisol indices are modifiable with targeted stress-related interventions.

Another consideration for stress-related interventions is targeting low-resilience individuals who may be struggling to cope with the stress in their lives. Resilience-building interventions among African Americans with T2D show promise in improving diabetes-related outcomes (Steinhardt et al., 2015; Steinhardt, Mamerow, Brown, & Jolly, 2009). However, there are a dearth of rigorous, evidence-based resilience-building programs focusing on prevention of cardiovascular and metabolic disease. Special consideration for tailoring such interventions should be given to the type (e.g., objective vs. subjective), duration (e.g., chronic vs. acute), and context (e.g., interpersonal vs. work-related) of the stress most commonly experienced by intervention participants given that cultivating resilience may be more beneficial for specific types of stress than others.

Appendix

Supplementary Table. Additional descriptive information of the study sample and breakdown by race/ethnicity.

	Full Sample (N = 228)	White (n = 73)	Hispanic (n = 86)	African American (n = 69)	*F* or χ^2
Demographic and lifestyle characteristics					
Age, years	45.29 (14.00)	42.48 (14.98)	44.42 (12.04)	49.33 (14.58)	4.81**
Sex, n female (%)	155 (68)	41 (56)	59 (69)	54 (78)	7.20*
Annual household income, n > $40k/yr (%)	103 (45)	49 (67)	25 (29)	29 (42)	12.13***
Educational attainment, n college degree (%)	70 (31)	44 (60)	10 (12)	16 (23)	16.92***
Blood pressure medication, n yes (%)	38 (17)	6 (8)	7 (8)	25 (36)	27.37***
Diabetes medication, n yes (%)	25 (11)	2 (3)	8 (9)	15 (22)	12.72**
Cholesterol medication, n yes (%)	21 (9)	5 (7)	9 (11)	7 (10)	0.63
Days of $\geq$ 30 min physical activity per week	3.49 (2.12)	4.08 (1.94)	3.52 (2.17)	2.81 (2.06)	6.67**
Psychological Measures					
Emotional Stability	5.09 (1.38)	5.21 (1.20)	4.92 (1.48)	5.19 (1.43)	1.87
Perceived Stress	1.23 (0.73)	1.15 (0.71)	1.26 (0.73)	1.26 (0.75)	1.15
Resilience	3.55 (0.72)	3.65 (0.75)	3.34 (0.71)	3.64 (0.68)	1.03
Hair-related characteristics and hair cortisol					
Hair Washes per week	4.02 (2.64)	4.63 (2.02)	5.50 (2.54)	1.54 (1.24)	73.21***
Conditioner, n yes (%)	176 (77)	51 (70)	64 (74)	61 (88)	6.38*
Bleach, n yes (%)	49 (22)	8 (11)	30 (35)	11 (16)	17.33***
Permanent Wave, n yes (%)	27 (12)	1 (1)	4 (5)	22 (32)	38.31***
Straightening, n yes (%)	62 (27)	5 (7)	28 (33)	29 (42)	23.86***
Hair cortisol, pg/mg, median (IQR)	7.9 (13.5)	6.0 (7.2)	8.2 (9.0)	8.6 (21.2)	2.79
Anthropometric and cardiometabolic parameters					
Total cholesterol, mg/dL, median (IQR)	176 (49)	183 (43)	186 (47)	160 (56)	6.15**
HDL cholesterol, mg/dL	52.36 (15.00)	54.33 (15.76)	51.06 (14.01)	51.87 (15.27)	0.99
LDL cholesterol, mg/dL	94.18 (28.86)	99.19 (28.42)	95.98 (27.04)	86.65 (30.37)	2.6
Triglycerides, mg/dL, median (IQR)	135 (121)	122.5 (114)	170 (121)	110 (98)	13.94***
Glucose, mg/dL, median (IQR)	99 (27)	98 (20)	100 (26)	100 (43)	2.4
A1C, mmol/mol, median (IQR)	5.5 (0.6)	5.3 (0.4)	5.5 (0.6)	5.6 (1.1)	9.56***
BMI, kg/m^2	29.71 (6.36)	27.30 (6.31)	29.84 (4.94)	32.2 (7.1)	11.48***
WHR	0.88 (0.08)	0.87 (0.08)	0.89 (0.07)	.89 (.09)	1.66
Systolic Blood Pressure, mmHg	122.33 (16.44)	120.11 (15.35)	122.03 (16.53)	125.04 (17.26)	1.99
Diastolic Blood Pressure, mmHg	75.40 (10.71)	74.47 (10.91)	75.94 (10.04)	75.71 (11.37)	0.43
MetS Severity	0.45 (1.34)	0.00 (0.88)	0.51 (0.90)	0.83 (1.93)	6.60**

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